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КЛИНИЧЕСКАЯ ПАТОФИЗИОЛОГИЯ: ОСНОВЫ

Belyaeva L.Eu.

CLINICAL PATHOPHYSIOLOGY: THE ESSENTIALS

Пособие

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В издании рассматриваются вопросы патофизиологии заболеваний основных систем организма, а также обсуждаются патофизиологические основы диагностики, профилактики и лечения заболеваний человека.

Предназначено для студентов 3 и 4 курсов, изучающих дисциплины «Патологическая физиология» и «Клиническая патологическая физиология» на английском языке.

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ABBREVIATIONS

A

β-AR, β-adrenergic receptor
ACE, angiotensin converting enzyme
ACTH, adrenocorticotropic hormone
AD, Alzheimer's disease
ADAMTS13, a disintegrin-like and metalloprotease with thrombospondin type 1 repeats
ADH, antidiuretic hormone
ADPKD, autosomal dominant polycystic kidney disease
AGEs, advanced glycated end products
AIDS, acquired immunodeficiency syndrome
ALS, amyotrophic lateral sclerosis
ALT, alanine aminotransferase
Ang, angiotensin
ANP, atrial natriuretic peptide
ANS, autonomic nervous system
APCs, antigen presenting cells
APT, activated partial thromboplastin time
ARDS, acute respiratory distress syndrome
ARF, acute renal failure
ARPKD, autosomal recessive polycystic kidney disease
AST, aspartate aminotransferase
ATN, acute tubular necrosis

B

BP, blood pressure
BUN, blood urea nitrogen

C

CAH, congenital adrenal hyperplasia
CBF, cerebral blood flow
CD, cluster of differentiation (designation)
CHD, coronary heart disease
CKD, chronic kidney disease
CK-MB, myoglobin isoenzyme of creatine kinase
CNS, central nervous system
CO, cardiac output
COPD, chronic obstructive pulmonary disease
COX, cyclooxygenase
CRH, corticotropin-releasing hormone
CRP, C-reactive protein
CSA, central sleep apnea

D

2,3-DPG, 2,3-diphosphoglycerate
DAMPs, damage associated molecular patterns
DDT, dichlorodiphenyltrichloroethane
DHEA(S), dehydroepiandrosterone (sulfate)
DIC, disseminated intravascular coagulation
DM, diabetes mellitus
DMT, divalent metal transporter
DOPA, 3,4-dihydroxyphenylalanine

E

ECG, electrocardiogram
EDLVP, end-diastolic left ventricular pressure
EDTA, ethylenediaminetetraacetic acid
EF, ejection fraction
ELISA, enzyme-linked immunosorbent assay
ENS, enteric nervous system
EPO, erythropoietin

ESR, erythrocytes' sedimentation rate
ESRD, end stage renal disease

F

FDPs, fibrin degradation products
FFAs, free fatty acids
FGF, fibroblast growth factor
FSH, follicle-stimulating hormone
FXR, farnesoid X receptor

G

GP, glycoprotein
γ-GTP, γ-glutamyl transpeptidase
GABA, γ-aminobutyric acid
GDH, glutamate dehydrogenase
GERD, gastroesophageal reflux disease
GFR, glomerular filtration rate
GH, growth hormone
GHRH, growth hormone-releasing hormone
GIT, gastrointestinal tract
GLP-1, glucagon-like peptide-1
GnRH, gonadotropin-releasing hormone
GSH, reduced glutathione
GSSG, oxidized glutathione

H

Hct, hematocrit
HDL, high-density lipoprotein
HF, heart failure
HIF, hypoxia-inducible factor
HIV, human immunodeficiency virus
HMG-CoA, 3-hydroxy-3-methylglutaryl-CoA
HR, heart rate
HSPs, heat shock proteins
HUS, hemolytic uremic syndrome

I

IBDs, inflammatory bowel diseases
IBS, irritable bowel syndrome
ICAM-1, intercellular adhesion molecule
IF, intrinsic factor
IFNγ, interferon-γ
IGF, insulin-like growth factor
IHD, ischemic heart disease
IL, interleukin
INR, international normalized ratio
IQ, intelligence quotient
IRDS, infant respiratory distress syndrome
IREs, iron regulatory elements
IRPs, iron regulatory proteins
ITP, idiopathic thrombocytopenic purpura
I.V., intravenously

L

LA, left atrium
LDH, lactate dehydrogenase
LDL, low density lipoprotein
LDLR, low density lipoprotein receptor
LES, lower esophageal sphincter
LH, luteinizing hormone
LOX, lipooxygenase
LOX, lipoxygenase
LTCC, L-type Ca^{2+} current
LTs, leukotrienes
LV, left ventricle

M

MAC, membrane attack complex
MAO, monoamine oxidase
MCHC, mean cellular hemoglobin concentration
MCV, mean cellular volume
MDH, malate dehydrogenase
MEN, multiply endocrine neoplasia

MHC, major histocompatibility complex
MRP, multidrug resistance protein
MS, multiply sclerosis

N

NADH, nicotinamide adenine dinucleotide (reduced)
NADPH, nicotinamide adenine dinucleotide phosphate (reduced)
NAFLD, non-alcohol fatty liver disease
NCX, Na^+/Ca^{2+} exchanger
NF-Kβ, nuclear factor Kappa β
NK-cells, natural killer cells
NMDA-receptors, receptors to the N-methyl-D-aspartate
NO, nitric oxide
NSAIDs, nonsteroidal anti-inflammatory drugs
NSTEMI, non-ST elevation myocardial infarction
NYHA, New York Heart Association

O

OSA, obstructive sleep apnea

P

PAH, pulmonary arterial hypertension
PAI, plasminogen activator inhibitor
PAMPs, pathogen associated molecular patterns
PARs, protease-activated receptors
PD, Parkinson's disease
PDGF, platelet derived growth factor
PGs, prostaglandins
PL A_2, phospholipase A_2
PMNs, polymorphonuclear neutrophils
PNS, parasympathetic nervous system
POMC, pro-opiomelanocortin
PPARγ, peroxisome proliferator activated receptors γ
PRL, prolactin
PRRs, pathogen-related receptors
PT, prothrombin time
PTH, parathyroid hormone

R

RAAS, renin angiotensin aldosterone system
RNS, reactive nitrogen species
ROS, reactive oxygen species
RBCs, red blood cells
RyR, ryanodine receptor

S

SERCA, Ca^{2+}-ATPase of the sarcoplasmic reticulum
SHBG, sex hormone binding globulin
SIAD, syndrome of inappropriate antidiuresis
SNS, sympathetic nervous system
SR, sarcoplasmic reticulum
STEMI, ST-elevation myocardial infarction
SV, stroke volume
SVR, systemic vascular resistance

T

T_3, triiodothyronine
T_4, tetraiodothyronine (thyroxine)
TF, tissue factor
TGF, transforming growth factor
TIA, transient ischemic attack
TLRs, Toll-like receptors
TNF, tumor necrosis factor
TRH, thyrotropin-releasing hormone
TSH, thyroid-stimulating hormone

TTP, thrombotic thrombocytopenic purpura
TX A_2, thromboxane A_2

U

UDP-GT, uridine diphosphate-glucuroniltransferase
UMP-GT, uridine monophosphate-glucuroniltransferase

V

VCAM-1, vascular cellular adhesion molecule-1
VEGF, vascular endothelial growth factor
VIP, vasointestinal peptide
VLDL, very low density lipoprotein
vSMCs, vascular smooth muscle cells
vWF, von Willebrand factor

W

WBCs, white blood cells
WHO, World Health Organization

CONTENTS

PART I. PATHOPHYSIOLOGY OF THE BLOOD

1. RED BLOOD CELLS DISORDERS

Changes of the total blood volume

Blood consists of a protein-rich fluid (plasma) and cellular elements (red blood cells, RBCs, white blood cells, WBCs, and platelets). The normal total circulating blood volume is about 8% of the body weight. The percentage of blood cells in the blood after blood sample centrifuging in a specialized tube is termed as hematocrit (Hct). For normal persons hematocrit is approximately 40-45%. Classification of blood volume disorders is presented in the Fig. 1-1.

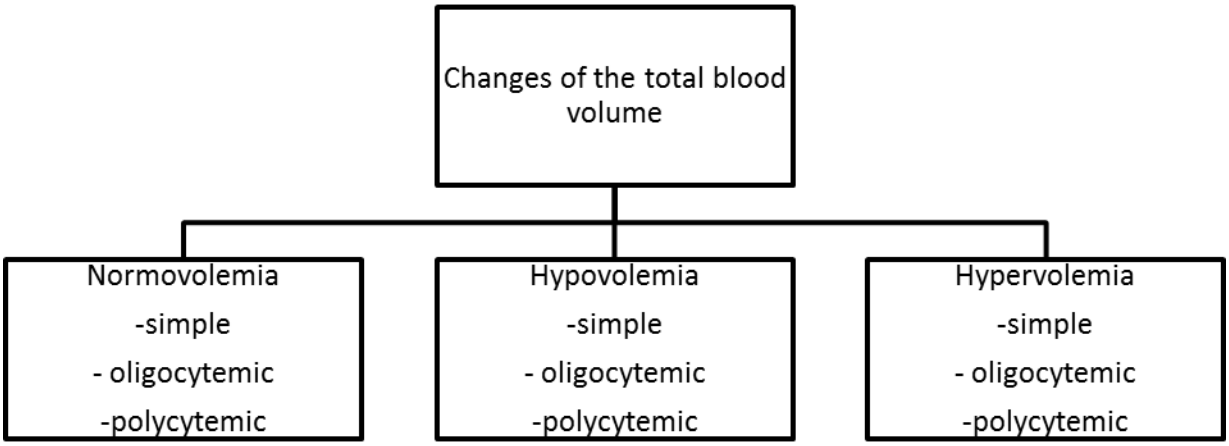


Figure 1-1. Blood volume disorders

Hypervolemia is defined as an increasing of the total blood volume.

Simple hypervolemia is characterized by unchanged Hct. Causes: transient state after a transfusion of a significant volume of the whole blood; intensive physical activity followed by translocation of the interstitial fluid and deposited blood in the blood vessels.

Oligocytemic hypervolemia is a result of an increasing of the plasma volume. Hct is decreased. Causes: disorders of kidneys, resolution of severe edema, transfusion of the crystalloids and colloids.

Policytemic hypervolemia is a result of an increasing total blood volume due to elevation of the red blood cells count. Hct is increased. Causes: mountain sickness, cardiac malformations (as a compensatory reaction in response to hypoxia), chronic myeloproliferative disorders.

Hypovolemia is a decreasing the total blood volume.

Simple hypovolemia is characterized by unchanged Hct. Causes: transient state immediately after severe acute hemorrhage or in the 1st stage of hypovolemic

shock (due to proportionally loss of both plasma and blood cells whereas compensatory mechanisms are not fully switch on yet).

Oligocytemic hypovolemia is a result of a depletion of the RBCs count. Hct is decreased. Causes: compensatory reactions developed after several hours in the posthemorrhagic period. These reactions are resulted from (1) autohemodilution and (2) increased synthesis of antidiuretic hormone (ADH) and aldosterone.

Policytemic hypovolemia is a result of decrease of total blood volume due to plasma loss predominantly. Hct is increased. Causes: dehydration of any etiology (diarrhea, vomiting, severe burns, overdose of diuretics, diabetes insipidus, etc).

Pathogenesis of hypovolemia is presented below.

Hypovolemia is more common disorder of the total blood volume and results from three groups of causes:

1. Fluid loss (hemorrhage, excessive perspiration, renal failure with polyuria, surgery, vomiting, diarrhea, nasogastric drainage, diabetes mellitus with polyuria or diabetes insipidus, fistulas, excessive use of laxatives, diuretic therapy, fever).
2. Reduced fluid intake (dysphagia, coma, environmental conditions preventing fluid intake, psychiatric illness).
3. Fluid shift from extracellular fluid (burns, acute intestinal obstruction, acute peritonitis, pancreatitis, crushing injury, pleural effusion, hip fracture).

Hypovolemia is an isotonic disorder. Fluid volume deficit decreases capillary hydrostatic pressure and fluid transport. Cells are deprived of normal nutrients that serve as substrates for energy production, metabolism, and other cellular functions. Decreased renal blood flow triggers the renin angiotensin system to increase sodium and water reabsorption. The cardiovascular system compensates by increasing heart rate, cardiac contractility, venous constriction, and systemic vascular resistance, thus increasing cardiac output and mean arterial pressure. Hypovolemia also triggers the thirst response, releasing more ADH and producing more aldosterone. When compensation fails, hypovolemic shock occurs in this sequence: decrease of intravascular fluid volume diminishes venous return, which reduces preload and decreases stroke volume, reduces cardiac output and decreases blood pressure → impairment of tissue perfusion → decrease of oxygen and nutrient delivery to cells → multiple organ dysfunction syndrome.

Symptoms of hypovolemia include orthostatic hypotension, tachycardia, thirst, flattened jugular veins, sunken eyeballs, dry mucous membranes, diminished skin turgor, rapid weight loss, decreased urine output and prolonged capillary refill time. Laboratory investigations detect increased blood urea nitrogen, elevated serum creatinine level, increased serum protein, hemoglobin, and hematocrit (unless caused by hemorrhage, when loss of blood elements causes subnormal values), rising blood glucose, elevated serum osmolality (except in hyponatremia, where serum osmolality is low). Serum electrolyte and arterial blood gas analysis may reflect associated clinical problems resulting from the underlying cause of hypovolemia or the treatment regimen. Urine specific gravity usually is more than

1.030 and associates with increased urine osmolality and decreased urine sodium level below than 50 mEq/L.

Pathophysiologic basis for hypovolemia correction: (1) oral fluids if possible; (2) parenteral fluids by rapid I.V. administration; (3) blood or blood products (with hemorrhage); (4) antidiarrheals as needed; (5) antiemetics as needed; (6) I.V. dopamine or norepinephrine to increase cardiac contractility and renal perfusion (if patient remains symptomatic after fluid replacement); (7) autotransfusion (for some patients with hypovolemia caused by trauma.

Anemia: definition and classification

Normal values obtained on automated blood-count-formed elements of so-called "red blood" are presented in the Table 1-1.

Table 1-1. Normal red blood cells parameters

	Normal males	Normal females
Hemoglobin, g/L	135-175	120-160
Red Blood Cells, count, $\times 10^{12}$/L	4.5-6.0	4.0-5.4
Mean cell volume (MCV), fL	81-99	
Mean cell hemoglobin concentration (MCHC), g/dL	30-36	
Colour index	0.9-1.1	
Reticulocytes, %	0.5-1.5	

Anemia is a syndrome which is characterized by a reduction in the hemoglobin concentration and/or red blood cells count below the normal range hemoglobin (in males - below than 130 g/L, in females - below than 120 g/L, in pregnant females - below than 110 g/l). Classification of anemia is given in the Table 1-2.

Table 1-2. General principles of anemia classification

Depending on the RBCs size	
Types	Examples
1. Macrocytic, with increased MCV	Vitamin B_{12}-deficiency anemia, folic acid deficiency anemia, liver diseases, alcoholism, hypothyroidism, some drugs
2. Microcytic, with decreased MCV	Iron deficiency anemia, some hemoglobinopathies including thalassemia
3. Normocytic, with normal MCV	Anemia of chronic disease, aplastic anemia, some forms of hemolytic anemia, anemia following acute hemorrhage
Depending on the red blood cells color	

1. Hyperchromic, with increased MCHC and colour index	Vitamin B12-deficiency anemia, folic acid deficiency anemia
2. Hypochromic, with decreased MCHC and colour index	Iron deficiency anemia, sideroblastic anemia, some cases of anemia of chronic disease, chronic posthemorrhagic anemia
3. Normochromic, with normal MCHC and colour index	Anemia of chronic disease
Depending on the basic pathogenetic mechanism	
1. Anemia due to blood loss	Anemia resulted from acute hemorrhage, chronic posthemorrhagic anemia as a result of repeated hemodinamically insignificant hemorrhages
2. Anemia resulted from increased RBCs destruction	Hereditary and acquired hemolytic anemia (see later)
3. Anemia caused by impaired RBCs production • Impaired heme synthesis • Impaired globin synthesis • Due to quantitive deficiency of hematopoietic progenitor cells • Impaired response to erythropoietin or decreased erythropoietin production • Caused by defective DNA synthesis in RBCs precursors	 Iron-deficiency anemia, sideroblastic anemia Thalassemia, severe protein deficiency Aplastic anemia, bone marrow replacement by neoplastic cells (myelophthisis) Anemia complicated chronic renal failure Vitamin B_{12}-deficiency anemia, folic acid deficiency anemia
4. Anemia caused by multiple mechanisms	Anemia of chronic disease
According to erythropoietic activity	
1. Hyperregenerative, with increased reticulocytes percentage	Acute posthemorrhagic anemia Reticylocytosis following hemolytic crisis
2. Hyporegenerative, with decreased reticulocytes percentage	Aplastic anemia Anemia caused by antibodies to erythropoietin
3. Dysplastic anemia	Anemia due to inability of erythrooid progenitors to respond to erythropoietin adequately
Based on etiology	
1. Hereditary	Hereditary spherocytosis, sickle cell disease
2. Acquired	Iron deficiency anemia, anemia of chronic disease, drug-induced hemolytic ane-

	mia
Depending on the severity	
1. Mild, when Hb is less than normal but more than 90 g/L	
2. Moderate, with Hb 70-90 g/L	
3. Severe, when Hb is lower than 70 g/L	

Compensatory mechanisms during anemia

The transport of oxygen is a product of three independent variables expressed in the Fick equation:

$$O_2 \text{ delivery} = \text{Blood flow} \times \text{Hb concentration} \times (A_{sat} - V_{sat}),$$

where A_{sat} – oxygen saturation in the arterial blood, V_{sat} – oxygen saturation in the venous blood. During anemia oxygen carrying capacity of the blood is low, so two remaining variables try to compensate compromised oxygen delivery:

1. Hemodynamic changes. In all anemic patients, there is redistribution of the blood flow to the heart, brain, liver, and kidneys, at the expense of nonvital organs. Anemic patients are pale because blood is diverted away from the skin and mucous membranes to preserve oxygen supply to the critical organs and due to decreased oxyhemoglobin concentration. Some patients have increased cardiac output. Cardiac output depends on stroke volume and heart rate. Hypoxia during anemia stimulates sympathetic activity thus leading to the tachycardia. Moreover, hypoxia and SNS activation stimulate activity of RAAS with sodium and water retention. Severe anemia often complicated with heart failure with increased cardiac output.
2. Shift of the oxygen binding for the hemoglobin curve to the right. Red blood cells of anemic patients have decreased oxygen affinity due to accumulation of 2,3-diphosphoglycerate in RBCs. This helps to compensate anemia.
3. Stimulation of erythropoiesis: anemia→hypoxia→HIF-1α activation→increased synthesis of erythropoietin in the kidneys→stimulation of proliferation and maturation of RBCs precursors.

Selected forms of anemia

Anemia due to blood loss

Acute blood loss in excess of 1500 mL usually leads to the hypovolemic shock (See book “General pathophysiology: the essentials, Part XVI). Following acute hemorrhage, the RBCs mass and plasma volume are contracted in parallel; accordingly, there is often not a significant decrease in the hemoglobin or hematocrit level initially. A moderate leukocytosis with a “shift to the left” in the white blood cells is common. In both acute and chronic blood loss, the platelet count is often increased, particularly if the patient is already iron deficient. During the first few days after acute blood loss, there is usually an increase in reticulocytes (Fig. 1-2, Supplement). The more filamentous reticula are characteristic of younger cells (brilliant cresyl blue stain).

Severe hypoxia may trigger the release of nucleated red cells from the bone marrow into the peripheral blood. Because young red cells are larger than old ones,

the MCV generally rises slightly. If significant blood loss continues, reticulocytosis will persist until iron stores have been exhausted. Internal bleeding is often accompanied by an increase in unconjugated bilirubin, reflecting an increase in the catabolism of heme from extravasated red blood cells. Patients with acute gastrointestinal blood loss sometimes have an elevation of blood urea nitrogen owing to impaired renal blood flow and perhaps to the absorption of digested blood protein. Patients with severe acute blood loss require resuscitation emergently.

Chronic blood loss leads to the iron deficiency anemia.

Iron deficiency anemia

To better understanding of pathophysiology of iron deficiency anemia it is necessary to overview metabolism of iron in the human organism.

Main functions of iron are:

- Oxygen transport (hemoglobin, myoglobin);
- Regulation of cellular proliferation and differentiation;
- DNA and RNA synthesis;
- Electron transport and cellular respiration;
- Redox-regulation of different cellular functions;
- Bactericidal activity;
- Cofactor of activity of enzymes (in citric acid cycle, porphyrin metabolism, melanin synthesis, serotonin synthesis, cytochrome P-450 and drug metabolizing system);
- GABA metabolism, myelinization.

Total iron stores in the organism are distributed in the following way (Fig. 1-3):

The control of systemic iron levels occurs through the regulation of iron acquisition and storage because there is no known regulated form of iron excretion. Normal iron loss in humans occurs through exfoliation of enterocytes and skin cells, and through sweat excretion. Small part of iron is excreted through the bile after red blood cells hemolysis. Menstruation and childbirth are significant ways of iron loss in females. That's why total amount of iron losses in healthy females are greater (2-3 mg per day) than in males (1-2 mg per day). Iron balance is maintained by iron acquisition, which can be increased in response to need. The absorption of dietary iron which may be in the heme form (Fe^{2+}) or in the non-heme, inorganic form (Fe^{3+}) is highly regulated (Fig. 1-4). Mixed meal contains 15-20 mg of iron, but absorbed daily only 10-15% of these iron. Heme iron in the meat meal is better absorbed than non-heme iron. Different additive substances in the food can or improve (ascorbic acid, citric acid, another inorganic acids, nicotinamide, cysteine, fructose) or suppress (tanins, carbonates, silicates, phosphates, EDTA, antacids, tetracyclines) absorption of non-heme iron. Iron is absorbed by the proximal part of the small intestine predominantly.

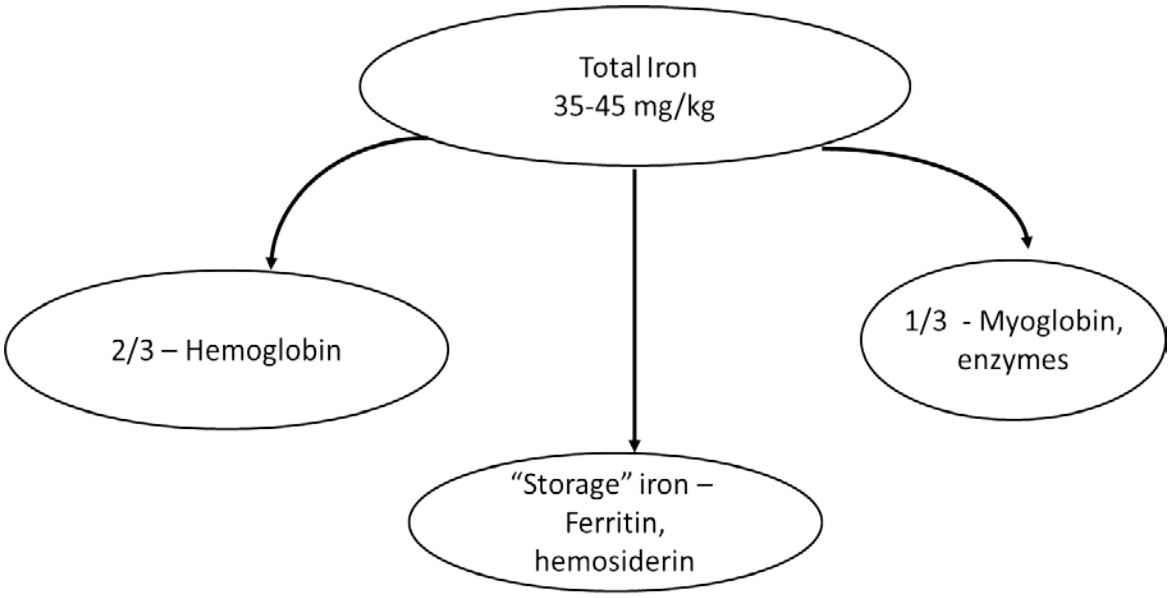


Figure 1-3. Distribution of the iron in the organism

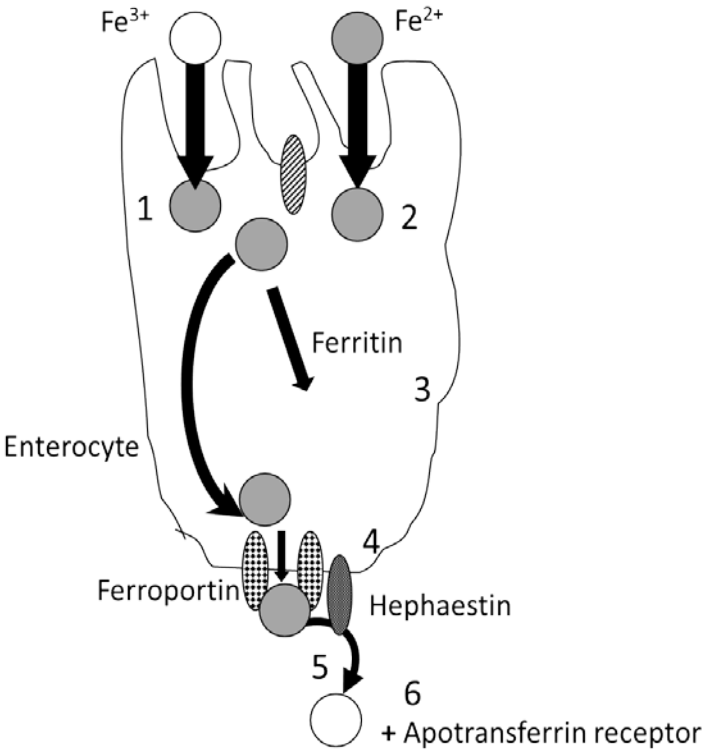


Figure 1-4. Steps of iron absorption

1. Ferric iron (Fe^{3+}) in the diet is converted to ferrous iron (Fe^{2+}) by a ferroreductase (Dcytb) that is located on the apical surface of enterocytes of the duodenal mucosa.
2. Fe^{2+} is then transported into enterocytes through the divalent metal transporter DMT1.

3. Fe^{2+} in enterocytes can be incorporated into the cytosolic iron-storage molecule ferritin or
4. Fe^{2+} can be transported across the basolateral surface of enterocytes into the plasma by ferroportin.
5. Fe^{2+} is subsequently converted to Fe^{3+} by a membrane-associated ferroxidase, hephaestin.
6. In the plasma, iron is bound to the glycoprotein transferrin which moves iron towards cells that express transferrin receptors.

Transferrin receptor is expressed on all dividing cells and is particularly enriched on precursors of the erythron. Senescent erythrocytes are ingested by macrophages and degraded in lysosomes; the iron that is released from catabolized haem enters the macrophage cytosol, where it can be stored in ferritin or exported by ferroportin. In normal conditions iron losses and iron absorption are in the balance because iron acquisition and storage are highly regulated by transcriptional and post-transcriptional mechanisms at both the cellular and systemic levels. The mechanism of post-transcriptional control of ferritin and transferrin receptors involves iron-regulatory proteins (IRPs). When iron is limiting, IRPs bind iron-regulatory elements (IREs), which are stem-loop structures that are found in non-coding regions of messenger RNAs and encode proteins involved in iron metabolism. The binding of IRPs to IREs in the 5′-untranslated regions of mRNA blocks translation, whereas binding in the 3′-untranslated regions stabilizes the mRNA and prevents degradation. Increased iron levels favor the conversion of IRP from its active RNA-binding form to aconitase, an enzyme that contains an iron-sulphur cluster, and this inhibits its IRE-binding activity. Moreover, after being exposed to a large dose of iron, enterocytes become refractory to absorbing more iron, a phenomenon referred to as mucosal block. It might reflect changes in the levels of DMT1 to prevent further iron uptake.

Iron absorption is regulated systemically. For example, iron absorption is increased in response to ineffective erythropoiesis or hypoxia. Another control is a decrease in iron export to plasma in response to inflammation, in which inflammatory cytokines regulate the synthesis of hepcidin. It is a circulating peptide hormone that regulates the entry of iron into plasma. Hepcidin is a member of the family of defensins (proteins with antibacterial and antiviral activity). Hepcidin is primarily secreted by hepatocytes. Hepcidin is a negative regulator of iron transport into plasma. It does so by binding to ferroportin, causing ferroportin to be phosphorylated, internalized, ubiquitylated, sorted through the multivesicular body pathway and degraded in lysosomes. Regulation of hepcidin expression seems to occur at the level of transcription, which can be modulated by anemia, hypoxia, inflammation and iron stores. Increased expression of hepcidin leads to decreased iron absorption and anemia.

Iron deficiency anemia is more common anemia word widely. More than 600 million are suffered from this anemia among all populations in the world. Latent iron deficiency is observed in 30% of humans.

Etiology of iron deficiency anemia:

1. Decreased iron absorption:
   - Dietary lack of iron and/or decrease of iron availability;
   - ↓ pH of gastric juice or treatment with antacid drugs;
   - Increase content of substances or drugs in the diet, which are able to impair intestinal absorption of the iron;
   - Elevated concentration of bivalent metals (Cu^{2+}, Pb^{2+}) in the diet (competition of these metals for their binding with DMT-1);
   - Increase enterocytes sloughing or their dysfunction following enteritis;
   - Resection of small intestine, especially its proximal part;
   - Celiac disease.
2. Increased blood loss:
   - Hemorrhages from gastrointestinal tract (gastritis, gastric ulceration, tumors, Meckel's diverticul, hemorrhagic diathesis, hemorrhoidal hemorrhage, parasitic diseases);
   - Elevated enterocyte sloughing (lactase insufficiency, enteritis);
   - Hemorrhages from genitourinary system (menorrhagia, tumors, chronic infectious diseases, endometriosis);
   - Hemorrhages from organs of respiratory system (hemosiderosis, tumors, infectious diseases);
   - Other hemorrhages (trauma, frequent blood donation, vascular malformations).
3. Increase iron requirement:
   - Pregnancy (iron deficiency anemia is diagnosed in 10% of pregnant females). Iron losses during pregnancy are approximately 700 mg. Iron requirement is rise from 16-20 weeks of gestation;
   - Lactation. Iron losses during 6 months of lactation are 250-300 mg;
   - Periods of intensive growth in children;
   - Pubertal development;
   - Excessive physical training.
4. Genetic disorders. The cloning of genes that are responsible for hereditary mouse anemias has resulted in the identification of many of the transporters or auxiliary proteins involved in iron acquisition. Human anemias are also expected to be the result of mutations of genes involved in iron acquisition; such genes would provide suitable candidates for these disorders (See information about iron homeostasis). For instance, hypotransferrinemia, also called atransferrinemia, is a condition in which little or no plasma transferrin is produced. This rare disorder leads to severe iron deficiency anemia accompanied by parenchymal iron overload.

Pathogenesis of iron deficiency anemia. Before development of iron deficiency anemia latent iron deficiency is manifested by changes in the biochemical blood analysis:

- Decreased concentration of iron in the serum (N – 12.5-30.0 mmol/l)

- Increased total iron-binding capacity (N – 45-62.5 mmol/l)
- Decreased saturation of transferrin by iron (N – 25-45%)
- Diminished serum concentration of ferritin (N – 30-300 ng/ml).

Peripheral blood smear during latent iron deficiency is unchanged. Astonishing of iron storage during this stage results in the repression of ferritin synthesis and activation of formation of transferrin receptors through interactions of IRPs with IRE of mRNA ferritin and transferrin receptors.

When negative iron balance increases and iron stores are completely depleted (low serum iron, ferritin, and transferrin saturation levels) synthesis of heme and globin is suppressed, erythropoiesis is slowed and hypochromic microcytic anemia develops (Fig. 1-5, Supplement). Most erythrocytes are smaller in diameter than the nucleus of a typical lymphocyte, and the area of central pallor is greater than 50% of the total diameter of the erythrocyte. Microscopic examination can reveal variations in red cell size (anisocytosis) or shape (poikilocytosis).

Because iron is a critical component of the porphyrin complex in muscle as well as many essential metabolic enzymes, its deficiency affects other organ systems besides the erythron (Table 1-3).

Table 1-3. Signs of iron deficiency anemia

Systems or organs	Changes
Blood	Microcytic hypochromic anemia
Cardiovascular system	Increase in cardiac output; redistribution of the blood flow; tachycardia; activation of RAAS; myocardial dysfunction; signs of heart failure during severe anemia
Skin and mucous membranes	Paleness; ↓ activity of hem-containing enzymes (prolinoxidase); alteration of cellular proliferation and differentiation → syderopenic syndrome (koilonychia, alopecia, angular stomatitis, glossitis, esophagitis)
Muscles	Impairment of hem synthesis; muscular dysfunction; ↓ work performance, urinary stress incontinence, dysphagia
Immune system	↓ activity of catalase, myeloperoxidase; ↓ lysozyme, complement, immunoglobulins, impairment activity of T- and B-cells → secondary acquired immunodeficiency
Central nervous system	↓ MAO activity, disorders of GABA metabolism, abnormal myelinization→ cerebral dysfunction; pica chlorotica (craving for unusual substances, such as a chalk, clay, uncooking meat, etc.)

Pathophysiological basis for the treatment of iron deficiency anemia. The treatment of iron deficiency anemia is replenishment of body iron stores with

different drugs containing salts of iron. In uncomplicated iron deficiency, oral iron supplementation produces an increase in reticulocytes in about 5 to 7 days that is followed by a steady increase in blood counts and the normalization of red cell indices. In situations in which primary blood loss is uncontrollable, iron cannot be absorbed owing to severe malabsorption, or oral iron is not tolerated, parenteral iron is an effective alternative treatment.

Anemia of chronic disease (anemia of chronic inflammation)

Anemia of chronic disease is believed to be the second most common cause of anemia, after iron deficiency anemia. Anemia of chronic disease varies in severity from mild to moderate. **Etiology** of anemia of chronic inflammation:

- Acute and chronic infections (viral infections, HIV, bacterial, parasitic, fungal);
- Autoimmune diseases, rejection after solid organ transplantation;
- Cancer (hematologic neoplasms, solid tumors);
- Inflammatory diseases (vasculitis, sarcoidosis, inflammatory bowel disease, chronic kidney diseases).

Mechanism of anemia of chronic disease is complex (Fig. 1-6).

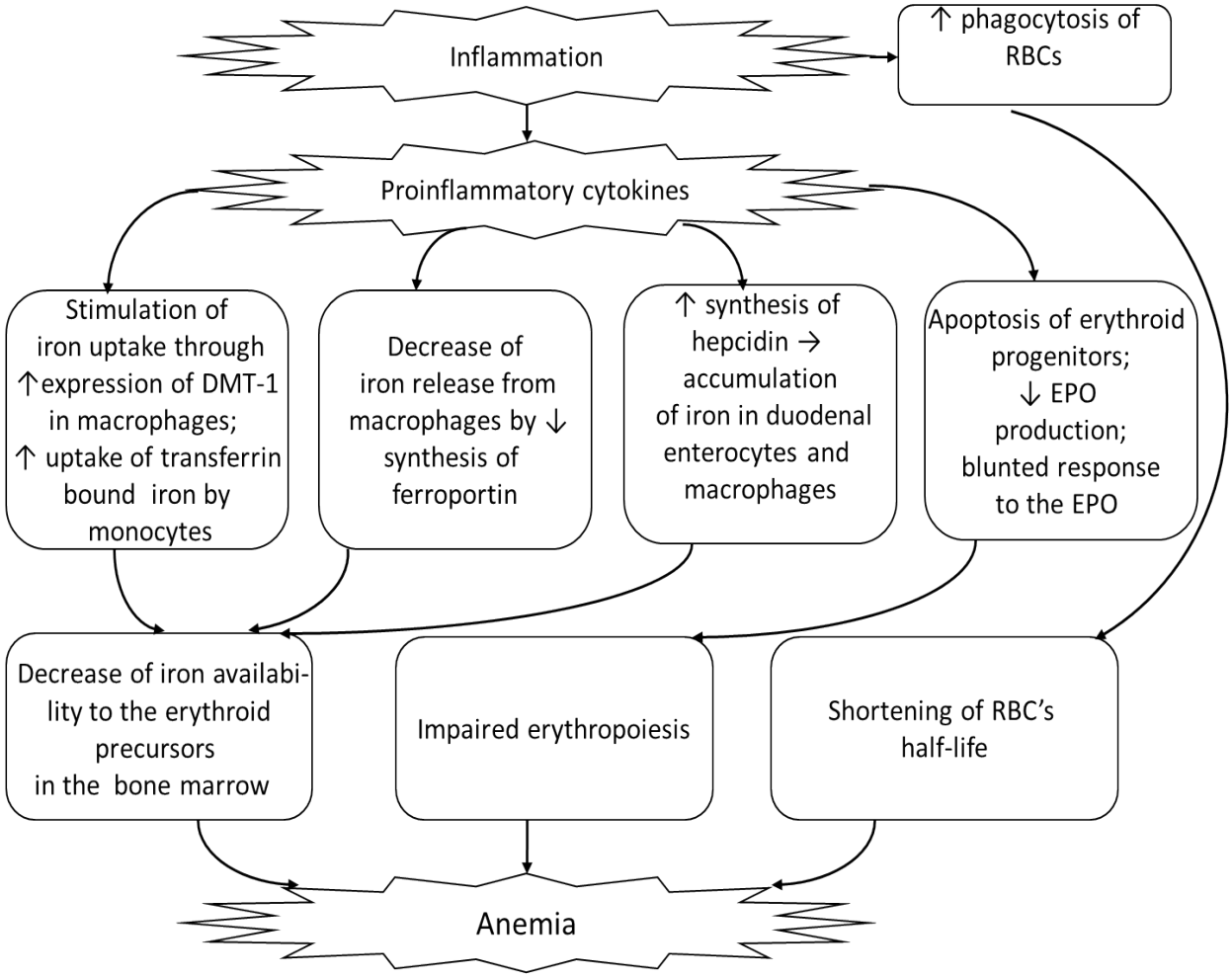


Figure 1-6. Pathogenesis of anemia of chronic disease

DMT-1, Divalent Metal Transporter; EPO, Erythropoietin; RBCs, Red Blood Cells

Hepcidin, an acute phase protein seems to play an important role in the development of iron deficiency anemia. Hepcidin stimulates accumulation of iron in duodenal enterocytes and reticuloendothelial macrophages due to the suppression of ferroportin in these cells. Thus hepcidin limits iron availability to the erythroid precursors.

Characteristic laboratory findings include low serum iron levels, low serum iron-binding capacity, increased serum ferritin, and normocytic or slightly microcytic erythrocytes. In contrast to patients with iron-deficiency anemia, those with anemia of chronic inflammation do not have elevated levels of serum transferrin receptor. Data illustrated in the Table 1-4 are useful for the evaluation of anemia of chronic disease.

Table 1-4. Differences between iron deficiency anemia and anemia of chronic disease

Laboratory Tests (concentration in the blood serum)	Iron deficiency anemia	Anemia of chronic diseases
Iron	↓	↓ or N
Transferrin	↑	↓ or N
Transferrin Saturation	↓	↓ or N
Ferritin	↓	N or ↑
Soluble Transferrin Receptor	↑	N

Anemia of chronic disease has both positive and negative significance. Firstly, decreased hemoglobin concentration in the blood in patients with inflammation may disturb growth and replication of microorganisms thus enhancing innate antimicrobial strategy. Secondly, proliferation of neoplastic cells is perturbed in anemic patient with cancer. Thirdly, decreased viscosity of the blood facilitates pumping of the blood by the heart and improves myocardial perfusion. Moreover, during anemia decreased margination of platelets and declined scavenging of NO help to reduce risk of thrombosis. On the other hand, anemia of chronic disease associates with impairment of macrophages activity, decrease macrophages' response to the cytokines; impaired phagocytosis which lead to secondary immunodeficiency and hypoxia.

Pathophysiologic basis for the treatment of anemia of chronic disease. Patients seldom require RBCs transfusions. Some patients may benefit from recombinant erythropoietin therapy. The anemia is not fully corrected unless the underlying disease is effectively treated. Treatment of mild to moderate anemia of chronic disease with iron-containing drug may increase mortality.

Pathogenesis of **anemia in patients with chronic renal failure** (chronic kidney disease) is presented in the Fig. 1-7.

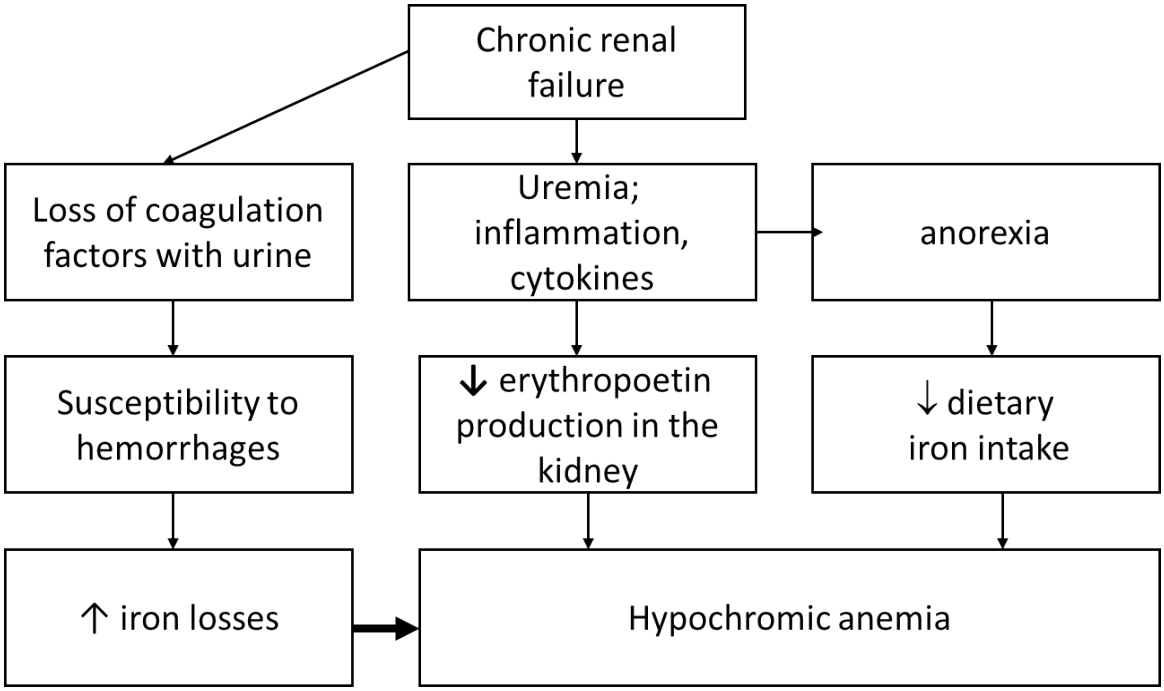


Figure 1-7. Mechanisms of anemia complicated chronic renal failure (chronic kidney disease)

It is important to know that erythropoiesis in normal conditions is stimulated by thyroxine, glucocorticoids, growth hormone and testosterone. That is why endocrine diseases with hypofunction of endocrine glands often associate with anemia (Table 1-5).

Table 1-5. Causes and mechanisms of anemia complicated endocrine disorders

Etiology	Pathogenesis
Hypothyroidism	1. Suppression of erythropoiesis caused by thyroxine deficiency; 2. Autoimmune thyroiditis with hypothyroidism may associate with autoimmune gastritis and impaired absorption of vitamin B_{12}; 3. Autoimmune thyroiditis may combine with immune-mediated hemolytic anemia; 4. Associated with hypothyroidism menorrhagia and dysfunctional uterine bleeding lead to secondary

	posthemorrhagic iron-deficiency anemia.
Adrenal insufficiency	Suppression of erythropoiesis caused by glucocorticoids deficiency or immune-mediated hemolysis in case of immune-mediated adrenal glands insufficiency.
Male hypogonadism	Suppression of erythropoiesis caused by testosterone deficiency

These types of anemia are well corrected after adequate hormone-replacement therapy.

Sideroblastic anemia

This heterogeneous group of anemias is characterized by excessive mitochondrial iron stores in erythroblasts and anemia. Sideroblastic anemia results from mitochondrial defects either in the biosynthesis of the heme porphyrin ring or in the metabolism of iron. Both hereditary (rare) and acquired types of sideroblastic anemia have been described. Inherited forms include X-linked sideroblastic anemia and sideroblastic anemia with autosomal-recessive, autosomal-dominant or mitochondrial type of inheritance. For better understanding of pathogenesis of sideroblastic anemia it is necessary to recall steps of heme synthesis:

- Glycyne+succinyl-CoA (in the presence of pyrydoxalphosphate) → δ-aminolevulinic acid (catalyzed by δ-aminolevulinic acid synthase);
- Conjugation of 2 molecules of δ-aminolevulinic acid to porphobilinogen.
- 4 pyrrole rings → porphyrin;
- Porphyrin → protoporphyrin IX;
- Protoporphyrin IX + Fe^{2+} → heme (catalyzed by ferrochelatase).

X-linked sideroblastic anemia results from mutations of gene encoding δ-aminolevulinic acid synthase on the X chromosome. The other forms of X-linked sideroblastic anemia results from defects in the ATP-binding cassette protein involving in iron-sulfur [FeS] cluster formation. This impairs adequate incorporation of iron into the heme porphyrin ring by ferrochelatase. Exact mechanisms of autosomal sideroblastic anemia are not fully understood. Mutations in the mitochondrial genome with maternal type of inheritance also may cause inherited sideroblastic anemia.

Causes of acquired sideroblastic anemia are: vitamin B_6 deficiency; lead intoxication; idiopathic sideroblastic anemia. Pyridoxin deficiency is the most common cause of sideroblastic anemia due to impairment of heme synthesis. Pyridoxine deficiency results from:

1. Treatment of tuberculosis with isoniazid. Isoniazid interacts with pyrydoxal and decreases activity of pyridoxal kinase with subsequent astonishing pool of the active form of pyridoxal-phosphate.
2. Carcinoid syndrome in colon cancer. Increased synthesis of serotonin by tumor cells associates with increased consumption of vitamin B6.
3. Dysbiosis, when synthesis of vitamin B6 by microbiota is impaired.

4. Alcoholism. Ethanol is an antagonist of the interaction of pyridoxal phosphate with 5-aminolevulinic acid as a cofactor in the 1st step of heme biosynthesis.

Lead intoxication results in the sideroblastic anemia via different mechanisms:

- Pb+SH-groups of aminolevulinic acid dehydrase and heme synthase → decrease synthesis of protoporphyrin and heme and accumulation of iron in the blood;
- Disorders of synthesis of α-chain of globin;
- Suppression of Na^+/K^+-ATPase activity in erythrocytes → osmotic lysis of erythrocytes;
- Decrease activity of pyrimidine-5-nucleotidase.

Pathogenesis of sideroblastic anemia can be presented schematically (Fig. 1-8).

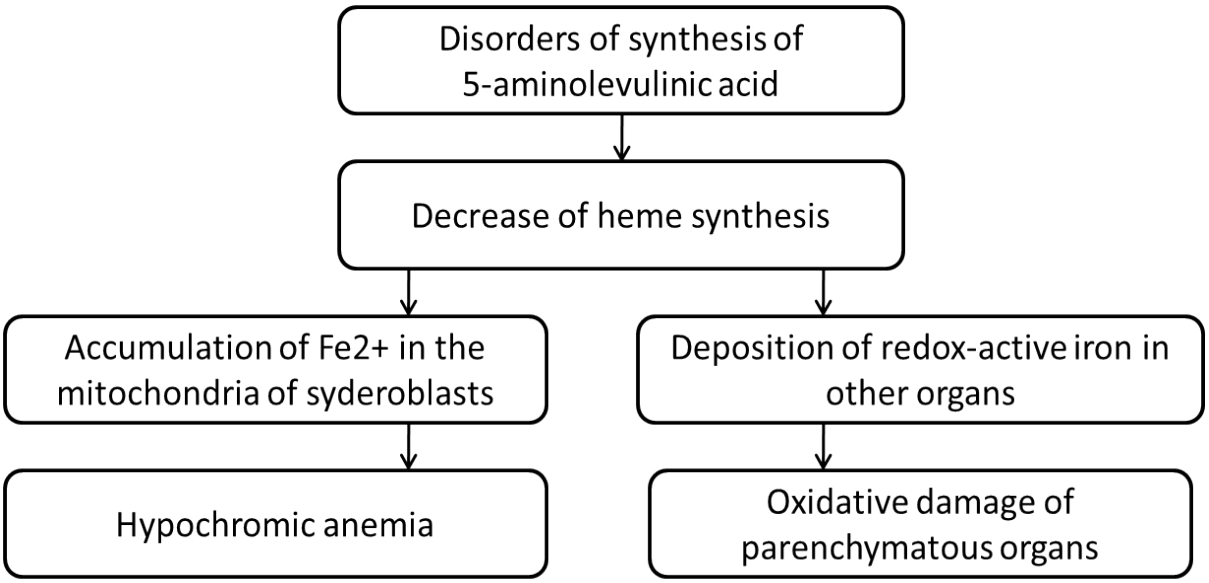


Figure 1-8. Simplified mechanism of sideroblastic anemia

Peripheral blood smear in patients with sideroblastic anemia is characterized by hypochromic erythrocytes, sometimes with basophilic stippling, and microcytosis. Prussian blue iron staining of the bone marrow aspirate helps to reveal abnormally large and numerous bluish siderosomes (mitochondria loaded with iron) within erythroblasts. These cells are called ringed sideroblasts (Fig. 1-9, Supplement). Biochemical blood analysis documents normal iron stores or evidence of iron overload.

Pathophysiologic basis for the treatment of sideroblastic anemia: (1) treatment of underlying cause; (2) pyridoxine replacement, if necessary; (3) bone marrow transplantation in inherited causes; (4) iron-chelation therapy in case of documented iron overload.

Megaloblastic anemia: vitamin B_{12}-deficiency anemia and folate-deficiency anemia

Vitamin B_{12} (cobalamin) is synthetized by certain bacteria in the gastrointestinal tract of animals and is then absorbed by the host animal. Vitamin B_{12} is concentrated in animal tissues, hence, vitamin B_{12} is found only in foods of animal origin. Foods that are high in vitamin B_{12} include: liver, beef and lamb, chicken, eggs and dairy foods. Vitamin B_{12} is bound to protein in food and is available for absorption after it has been cleaved from protein by the HCl produced by the gastric mucosa. The released cobalamin then attaches to R protein and passes into the duodenum where the R protein is removed and free cobalamin binds to Intrinsic Factor (IF). The IF-cobalamin complex is absorbed by the distal ileum. Vitamin B_{12} enters the circulation about 3–4 hours later bound to transcobalamins. Complete vitamin B_{12} deficiency develops slowly, even after total achlorhydria and loss of intrinsic factor occur. Liver stores of vitamin B_{12} are adequate for several years.

Vitamin B_{12} comprises a number of forms including cyano-, methyl-, deoxyadenosyl- and hydroxy-cobalamin. The cyano form, which is used in supplements, is found in trace amounts in food. The other forms of cobalamin can be converted to the methyl- or 5-deoxyadenosyl forms that are required as co factors for methionine synthase and L-methyl-malonyl-CoA mutase. Methionine synthase is essential for the synthesis of purines and pyrimidines. The reaction depends on methyl cobalamin as a co-factor and is also dependent on folate, in which the methyl group of methyltetrahydrofolate is transferred to homocysteine to form methionine and tetrahydrofolate. A deficiency of vitamin B_{12} and the interruption of this reaction lead to the development of megaloblastic anemia due to disorders of DNA synthesis. Folate deficiency independent of vitamin B_{12} also causes megaloblastic anemia. Methylmalonyl CoA mutase converts methylmalonyl CoA to succinyl CoA, with 5-deoxyadenosyl cobalamin required as a cofactor. It is a defect in this reaction, and the subsequent accumulation of methylmalonyl CoA that is thought to be responsible for the neurological effects in vitamin B_{12} deficiency resulted from impaired myelinization.

Causes of vitamin B_{12}-deficiency anemia are discussed in the Table 1-7.

Table 1-7. Etiology of vitamin B_{12}- deficiency anemia

Groups of causes	Explanations
Dietary inadequacy	Vegans or ovo-lacto vegetarians with poor diets are in the risk group for the development of vitamin B_{12} deficiency.
Impairment of vitamin B_{12} absorption	Total gastrectomy; Inadequate pancreatic protease (R factor– cobalamin not degraded, cobalamin not transferred to intrinsic factor); Inadequate IF production (atrophic gastritis) results in the pernicious anemia; Formation of antibodies against IF (autoimmune

	diseases); Decreased HCl secretion (atrophic gastritis); Impairment of the ileal uptake of vitamin B_{12} due to diseases affecting intestine (Crohn's disease, other chronic bowel inflammatory conditions); Intestine resection; Competition for vitamin B_{12} in patients with bacterial overgrowth or parasitic infections; Drug-nutrient interactions (proton pump inhibitor medications, metformin, nitrous oxide anaesthesia, some epileptic medications and colchicine); as well as some less common genetic defects
Increased metabolic demand for vitamin B_{12}	Pregnant and/or lactating women following vegetarian or vegan diets are at high risk of deficiency.
Rare genetic causes	Defective transcobalamine II, which is responsible for cobalamine transport in plasma and for its uptake into cells.

All specters of disorders related with deficiency of vitamin B_{12} are schematically presented in the Fig. 1-10.

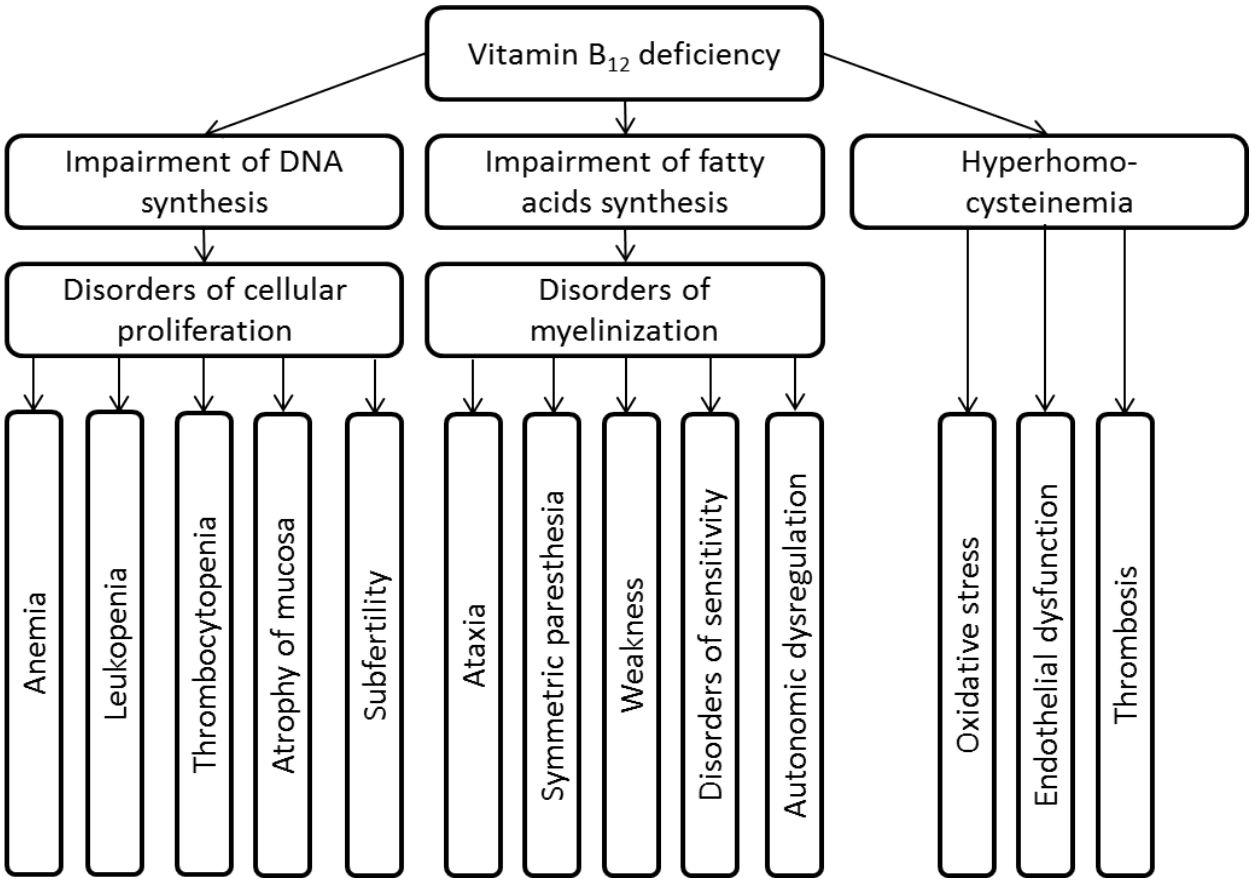


Figure 1-10. Consequences of deficiency of vitamin B_{12}

The interaction between folate and B_{12} is responsible for the megaloblastic anemia seen in both vitamin deficiencies. Dyssynchrony between the maturation of cytoplasm and that of nuclei leads to macrocytosis, immature nuclei (with Howell-Jolly bodies and Cabot rings), and hypersegmentation in granulocytes in the peripheral blood (so-called "shift to the right"). Howell-Jolly bodies consist of nuclear remnants. Cabot rings are remnants of spindle fibers in RBCs (Fig. 1-11, Supplement). The hypercellular and dysplastic bone marrow can be revealed. In contrast to the normally dense chromatin of comparable normoblasts, megaloblastic erythroid precursors have an open, stippled, reticular, sieve-like pattern. The orthochromatic megaloblast, with its hemoglobinized cytoplasm, continues to retain its large, sieve-like immature nucleus. The significant part of megaloblastic cells die in the bone marrow and are scavenged by macrophages in a process called ineffective erythropoiesis or intramedullary hemolysis. The ineffective erythropoiesis results in intramedullary hemolysis and release of lactate dehydrogenase. Proliferation of all hematopoietic lines disturbs thus causing leukopenia and thrombocytopenia. Maturing of existing neutrophils results in segmentation of their nuclei with 7-9 segments. Decreased proliferative activity of epithelial cells leads to atrophic changes in mucosa membranes thus creating "vicious circle" in atrophic gastritis. Impaired gametogenesis in both females and males may lead to the subfertility.

Neurologic disorders which are characterized by gait disorders (ataxia), loss of sensitivity, paresthesia, weakness, optic nerve atrophy, loss of smell and taste, and others result from impaired myelinization due to abnormal fatty acids synthesis. The latter is resulted from 5-deoxyadenosyl cobalamin deficiency.

Accumulation of homocysteine associates with endothelial dysfunction and increased risk of thrombosis.

Pathophysiological basis for the treatment of vitamin B_{12}-deficiency anemia: oral or parenteral (in case of impairment absorption) vitamin B_{12} introduction in the organism.

The best sources of **folate** are fresh uncooked vegetables and fruits. Food folates are mainly in polyglutamate form and must be destroyed for intestinal microorganisms for absorption in the upper third of small intestine. After absorption folates are transported as monoglutamate form with blood. In different cells enzyme dihydrofolate reductase converts dihydrofolate to tetrahydrofolate. The last is used for synthesis of purines and thymidilate which are important substrates for DNA formation. Causes of folate deficiency are listed in the Table 1-8.

Table 1-8. Etiology of folate deficiency

Groups of causes	Explanations
Dietary inadequacy	↓ intake (famine, psychiatric facilities, prolonged feeding of infants with goat's milk, cooking techniques – folate is destroyed following 10-15 minutes of cooking)
Increased require-	Physiological causes: pregnancy, lactation, infants,

ments+dietary inadequacy	preterm birth. Pathology: hematologic diseases with hemolysis and compensatory hyperregenerative erythropoiesis, bone marrow infiltration by malignant neoplasms; psoriasis (accelerated turnover of skin cells)
Impairment of folate absorption	Inhibition of proton-coupled folate transporters caused by drugs (sulfasalazine, pyrimethamine, proton pump inhibitors); Genetic causes: rare mutations in proton-coupled folate transporters genes; Damage of intestinal mucosa (tropical/nontropical sprue, enteritis).
Impairment of folate transport in the cerebrospinal fluid	Formation of autoantibodies to folate receptors (rare cause)
Inadequate cellular utilization	Folate antagonists (methotrexate inhibits dihydrofolate reductase) or hereditary enzyme deficiencies involving folate metabolism
Drug-induced folate deficiency due to multiply mechanisms	Ethanol, sulfasalazine, triamterene, pyrimethamine, trimethoprim-sulfamethoxazole, phenytoin, barbiturates

Folate deficiency leads to the impairment of DNA replication in all cell lines with high proliferative potential. That is why peripheral blood smear in folate deficiency anemia is like this in vitamin B_{12}-deficiency anemia and includes pancytopenia, macrocytosis, hyperchromia and hypersegmented neutrophils (see Fig. 1-11, Supplement). Despite this similarity, neurological abnormalities are not common for folate deficiency. Only cobalamin deficiency results in a demyelinating process.

Folate-replacement therapy (oral administration of folic acid) is a cornerstone for the **pathogenetic treatment** of folate deficiency anemia.

Aplastic anemia

Aplastic anemia is characterized by the empty bone marrow. All hematopoietic cells are markedly reduced. Aplastic anemia may be inherited (rare) and acquired, which is presented most commonly. Rare hereditary bone marrow failure syndromes are Fanconi anemia, dyskeratosis congenita, and Diamond-Blackfan anemia. Fanconi anemia is caused by mutations of genes encode proteins which protect the genome from damaging substances. Different chemical agents are triggers initiating premature death of hematopoietic cells in the bone marrow. The genetic base of dyskeratosis congenita is mutated genes which are responsible for the maintenance of telomeres length. That is why in the latter case hematopoietic cells

die prematurely from excessive apoptosis. In Diamond-Blackfan anemia inactivating mutations involve ribosomal proteins which are necessary for the ribosome biogenesis.

Causes of acquired aplastic anemia are following:

- Ionizing radiation, which causes direct injury of DNA of hematopoietic cells;
- Viral infections (caused by Hepatitis viruses, Epstein-Barr virus);
- Cytotoxic drugs in the dose-dependent manner (antineoplastic drugs including antimetabolites, alkylating and cross-linking drugs, cytotoxic antitumor antibiotics, plant alkaloids, topoisomerase inhibitors; antimicrobial agents such as chloramphenicol and dapsone; anti-inflammatory drug colchicine);
- Different chemicals (insecticides, benzene or benzene-containing chemicals);
- Idiosyncratic, dose-independent immune reactions against some antimicrobial drugs, antihistamine drugs, anticonvulsants, anti-inflammatory drugs, some diuretics, some antihypertensive drugs and some sedative drugs;
- Some autoimmune diseases;
- Idiopathic (with unknown origin aplastic anemia).

Basic mechanism of aplastic anemia is an injury of pluripotent hematopoietic stem cells. This injury may be immune or non-immune mediated. Immune-mediated damage of pluripotent stem cells is resulted from action of both cytotoxic T-lymphocytes and cytokines with myelosuppressive action, such as TNF-α and IFN-γ. This mechanism of aplastic anemia is more common for idiosyncratic (dose-independent) adverse drug reaction.

Peripheral blood smear in patients with aplastic anemia is characterized by pancytopenia (decreased RBCs', leukocytes and platelets count). Bone marrow biopsy helps to establish the diagnosis. Only some residual lymphoid cell without nonlymphoid hematopoietic cells populations can be found in marrow specimens. If the hematopoietic marrow has been replaced by neoplastic cells, the diagnosis of aplastic anemia cannot be made.

Pathophysiologic basis for therapy of aplastic anemia. Mild forms of aplastic anemia do not require aggressive therapy. Blood components transfusions are indicated. Inherited forms of aplastic anemia need in the bone marrow transplantation early in life. Immunosuppressive therapy is indicated for immune-mediated forms of aplastic anemia.

Hemolytic anemias

These types of anemias are resulted from increased premature destruction of RBCs (normal RBCs' lifespan is approximately 120 days) and are less frequent than anemia with decreased RBCs production. Classification of hemolytic anemias is introduced in the Fig. 1-12.

All hemolytic anemias have definite laboratory criteria (Table 1-9).

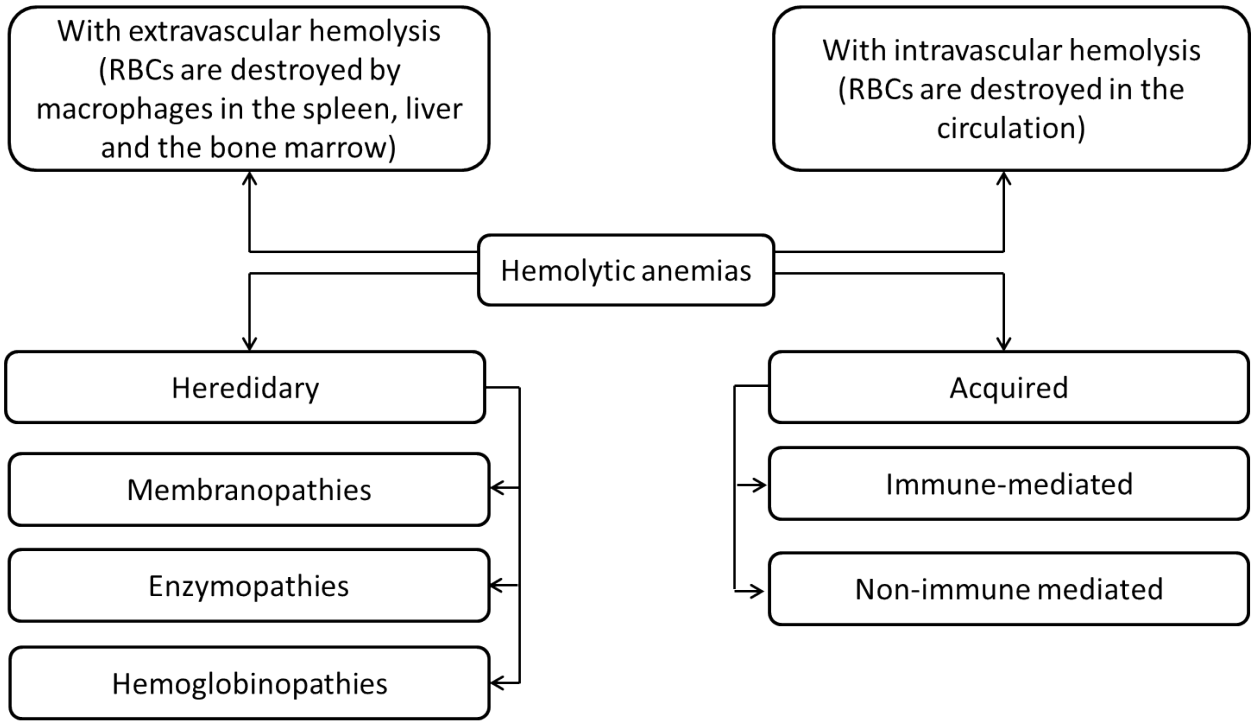


Figure 1-12. Classification of hemolytic anemias

Table 1-9. Signs common to hemolytic anemias

All hemolytic anemias are characterized by:	
• Decreased RBCs count; • Reticulocytosis (hemolysis of RBCs→hypoxia→EPO→stimulation of erythropoiesis); • Erythroid hyperplasia in the bone marrow; • ↑ of nonconjugated bilirubin concentration in the serum; • ↑ activity of LDH 1, 2 and 3 izoenzymes; • ↓ haptoglobin concentration in the blood serum (hemoglobin released from destroyed RBCs binds with haptoglobin and is cleared from the circulation. More severe decreasing of haptoglobin level is seen after intravascular hemolysis); • ↑ risk of gallstones; • Clinical signs of iron overload.	
Intravascular hemolysis	Extravascular hemolysis
• ↑↑↑ plasma Hb; • Hemoglobinuria (Hb passes from the renal filter and colors urine in the red or brown colour); • Hemosiderinuria	• ↑ plasma Hb

Hereditary membranopathies

Pathophysiologic characteristic of membranopathies with different type of inheritance is presented in the Table 1-10 (Supplement).

Hereditary enzymopathies

There are a net of ATP-dependent processes in mature erythrocytes: (1) glycolysis; (2) pumping of cations against electrochemical gradients; (3) maintenance of membrane phospholipids integrity; (4) maintenance of hemoglobin in its functional reduced (ferrous) state; (5) synthesis of antioxidants including glutathione; (6) protection of hemoglobin from ROS-mediated damage; and (7) nucleotide salvage reactions. Main sources of ATP in erythrocytes are most important Embden-Myerhof pathway and the hexose monophosphate shunt. Embden-Myerhof pathway uses glucose-6-phosphate, approximately 90% of which converts into lactate, pyruvate, and ATP (anaerobic pathway). This pathway also is a source of NADH used for the maintenance of hemoglobin in the reduced state. The Rapoport-Luebering shunt of the Embden-Meyerhof pathway produces 2,3-diphosphoglycerate (2,3-DPG) which regulates affinity of oxygen binding with hemoglobin. The remaining 10% of glucose-6-phosphate is directed to hexose monophosphate shunt (aerobic pathway) to produce reduced intermediates and ribulose 5-phosphate. The latter enters the Embden-Meyerhof pathway. Hexose-monophosphate shunt produces also NADPH for the subsequent reduction of oxidized glutathione.

Glucose-6-phosphate-dehydrogenase deficiency is the most common hereditary enzymopathy. However, patient with this disorder have an advantage against infection caused by Plasmodium falciparum. In the hexose-monophosphate shunt glucose-6-phosphate dehydrogenase converts NADP to NADPH. In affected males (due to X-linked type of inheritance) a lack of NADPH in mature erythrocytes leads to oxidative damage of their membrane after exposure of different oxidants, such as naphthalene, fava beans or antimalarial drugs, sulfonamides, nitrofuranes, some analgetics and some antihelmints. Affected males should avoid these substances. Oxidative-mediated damage of proteins and lipids in the erythrocytes membrane impairs their deformability and affected erythrocytes are damaged in the blood vessels of spleen and liver. Findings vary from asymptomatic to severe. Peripheral blood smear is characterized by normocytic normochromic anemia, anisocytosis, poikilocytosis and presence of Heinz bodies (oxidized denaturated, precipitated hemoglobin in the erythrocytes). The latter are seen as deep-blue, rounded, often eccentrically placed inclusion bodies after special staining (Fig. 1-13, Supplement).

Defects of glutathione metabolism involve lack of glutathione synthetase or γ-glutamylcysteine synthetase. Affected individuals have too low concentration of reduced glutathione (GSH) in RBCs. Chronic hemolytic anemia is resulted from increased susceptibility of membrane of erythrocytes to oxidative stress.

Pyruvate kinase deficiency is the second common hereditary enzymopathy after glucose-6-phosphate dehydrogenase deficiency. The type of inheritance is au-

tosomal recessive. Pyruvate kinase acts in the Emden-Myerhof pathway. This enzyme catalyzes the conversion of phosphoenolpyruvate to pyruvate for generation of ATP. Decreased pyruvate kinase activity associates with shrunken level of ATP in erythrocytes. As a result, impairs all ATP-dependent processes in RBCs, including maintenance of water and ion balance. That is why deformability of erythrocytes falls and hemolysis develops. Compensatory accumulation of 2,3-DPG in erythrocytes shifts the oxygen dissociation curve to the right thus partially compensating tissue oxygenation. Degree of hemolysis in affected patients varies.

Hereditary hemoglobinopathies

These types of anemias have common feature – impaired synthesis of globin. At least 300 variants of hemoglobin have been described. Most common clinically significant forms of hereditary hemogloglobinopathies include different forms of thalassemias and sickle cell anemia.

Normally hemoglobin (HbA1) consists of 2 α chains (of 141 amino acids each) and 2 β chains (of 146 amino acids). Only 2–3% of hemoglobin contains so-called δ-chains instead of the β-chains (HbA2). The α-chains are encoded by two α-globin genes, which lie in tandem on chromosome 11, while the β-chains are encoded by a single β-globin gene located on chromosome 16. Fetal hemoglobin (HbF) contains γ-chains instead of the β-chains. HbF has a higher O_2 affinity. This helps fetus to adapt to the intrauterine hypoxic condition. After birth HbF is replaced to HbA1 or HbA2.

Thalassemia is a group of hereditary hemolytic anemias characterized by defective synthesis of the globin chains. Thalassemias are most common in people of Mediterranean ancestry (especially Italian and Greek, who develop the form called β-thalassemia). People whose ancestors originated in Africa, southern China, south-east Asia, and India develop the form called α-thalassemia, which reflects deletion of one or more of four Hb genes. Prognosis varies with the number of deleted genes.

β-thalassemia is resulted from the mutations affecting synthesis of β-chain of hemoglobin. β0 variant characterizes by the absent of β-chain synthesis. In the β+ variant synthesis of β-chain is reduced. β-thalassemia occurs in three clinical forms: major, intermedia, and minor. The severity depends on whether the patient is homozygous or heterozygous for the thalassemic trait:

- Thalassemia major: patient has any two β0 and β+ alleles and seldom survive to adulthood;
- Thalassemia intermedia: patient has two β+ alleles. Such children develop normally into adulthood, however, puberty usually delayed;
- Thalassemia minor: patient inherits only one abnormal allele. Affected individuals have normal life span.

The impaired synthesis of β-globin leads to inadequate HbA formation, production of hypochromic and microcytic erythrocytes. Predomination of α-globin chain synthesis results in the aggregation of α-chains and formation of insoluble precipitates in the erythroblasts. Some such erythroblasts die from apoptosis prematurely in the

bone marrow (ineffective erythropoiesis). Survivor erythrocytes have a shortened life span due to extravascular hemolysis in the spleen and liver. Precipitated hemoglobin in mature erythrocytes in the peripheral blood gives them look of target cells (Fig. 1-14, Supplement). Ineffective hematopoiesis (with iron release from dying erythroblasts) and stimulation of iron absorption (partially mediated via low hepcidin level in thalassemia) during severe anemia lead to the iron overload and signs of secondary hemochromatosis. Increased erythropoietin level in anemic hypoxic patient stimulates extramedullary erythropoiesis (in the intramedullary space of the skeleton, spleen, liver and lymph nodes) producing bone and skull deformations, hepatomegaly, splenomegaly and lymph nodes enlargement (Fig. 1-15).

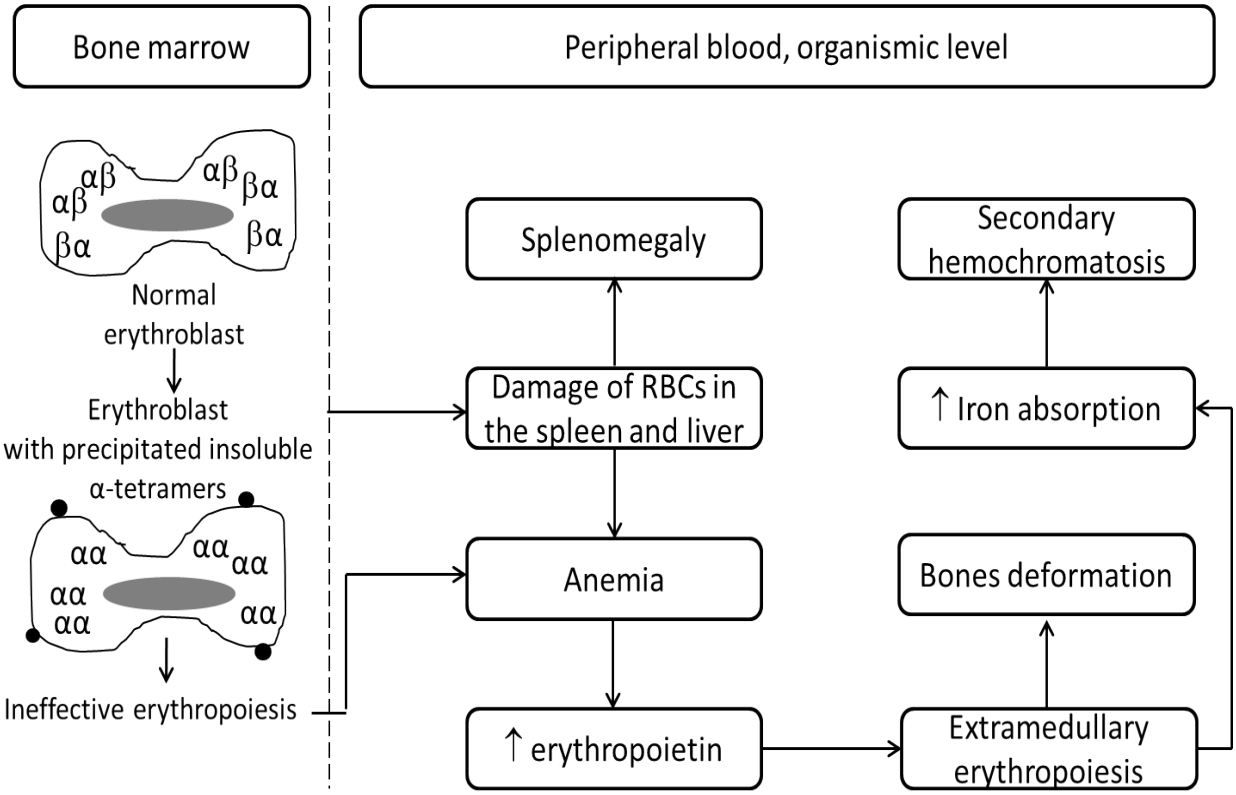


Figure 1-15. Mechanisms of pathologic changes in the organism in β-thalassemia major

α-thalassemia is characterized by a reduction quantity of α-globin chains. The clinical picture of α-thalassemia correlates with the number of affected α-genes. In α0 form both α genes are inactivated, whereas in α+ form only one of the pair is defective. In carriers of α0-thalassemia a few red cell HbH inclusions (β4) are formed. It is important to know that αo form (genotype −−/−−) is incompatible with life. Because α-globin chains are absent during gestation, Hb Bart's (γ4) becomes the dominant hemoglobin. It has high oxygen affinity thus unables to deliver oxygen to tissues. Developing hydrops fetalis syndrome leads to death either in utero or in the early postnatal period. Intermediate or mild forms of α-thalassemia

have high or slightly elevated, accordingly, levels of HbH and/or Hb Bart's with different RBCs count and signs of hemolysis.

Sickle cell anemia is caused by mutation of gene encoding β-globin chain. Sickle hemoglobin (HbS; α2β2S) is resulted from an adenine to thymidine substitution in codon 6 of the β-globin gene, with subsequent replacement of the glutamic acid residue by a valine in the β-chain of globin. This mutation is widespread in equatorial Africa, the Middle East, and India. An abnormal HbS has unique property to polymerization in deoxygenated state. Accumulation of polymerized HbS results in the change of erythrocytes' form with formation of sickle cells or drepanocytes (Fig. 1-16, Supplement).

Moreover, such polymers can have a direct impact on the RBCs' plasma membrane, leading to the extracellular exposure of protein epitopes and glycolipids that are normally found inside the cell. Dense sickle erythrocytes that become dehydrated after several rounds of sickling expose their annexin V-binding phosphatidyl serine on the outer layer of the plasma membrane. These negatively charged glycolipids can activate the coagulation cascade, leading to the generation of tissue factor and thrombin, which in turn promote the inflammatory response. Chronic extravascular hemolysis leads to the release of plasma-free hemoglobin, which can scavenge NO and causes endothelial dysfunction. The released heme iron leads to oxidative stress that can induce redox-sensitive transcription factors such as NF-kB and activator protein-1. These transcription factors in turn induce the expression of adhesion molecules and the recruitment of adherent leukocytes in venules. The presence of adherent leukocytes in small postcapillary venules is a key factor leading to painful vasoocclusion crisis. Sickle erythrocytes can interact directly with adherent leukocytes. Pathogenesis of sickle cell disease is illustrated below (Fig. 1-17).

<u>Pathophysiologic basis for treatment of hereditary hemoglobinopathies.</u> Nonspecific treatment is required for α- or β-thalassemia heterozygotes. The conventional treatment for thalassemia major and sickle cell anemia patients includes transfusion therapy and iron chelation. Many patients with hemoglobinopathies require splenectomy because of hypersplenism with subsequent correction of secondary immunodeficiency. Allogeneic hematopoietic stem cell transplantation in severe hemoglobinopathies has been increasingly successful during the last years. An alternative treatment of β-thalassemia and sickle cell anemia consists of the pharmacologic stimulation of HbF synthesis with hypomethylating agents, histone deacetylase inhibitors, and hydroxyurea. Gene therapy is an attractive approach for thalassemia syndromes.

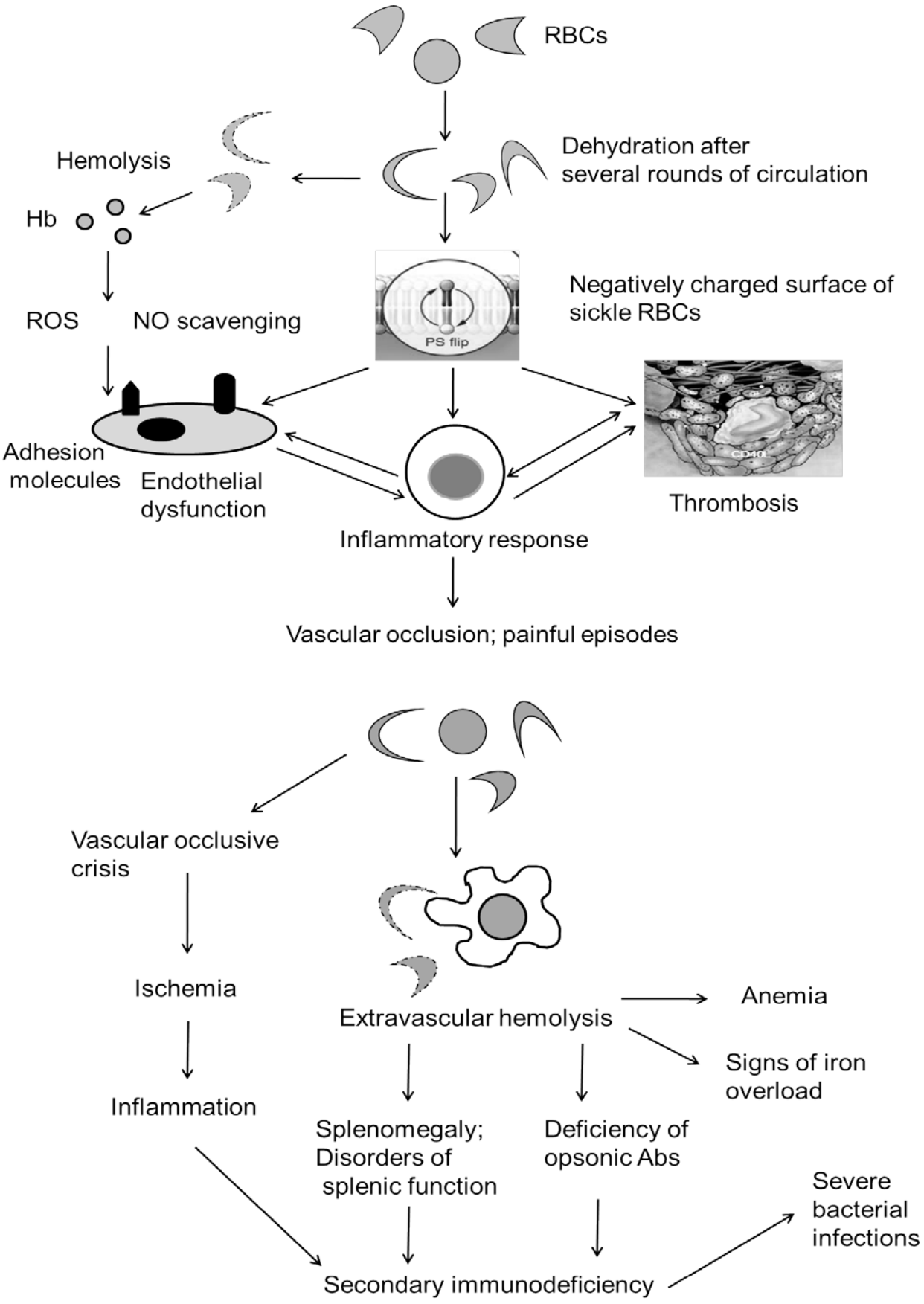


Figure 1-17. Pathogenesis of sickle cell disease

Abs, antibodies; Hb, hemoglobin; ROS, Reactive Oxygen Species

Acquired hemolytic anemias

Immune hemolytic anemias may be autoimmune or alloimmune (hemolytic transfusion reactions). These anemias are resulted from warm antibodies (commonly) or "cold" antibodies action. The term "warm" antibodies mean that these immunoglobulins G react best with RBCs at 37^0C. "Cold" antibodies (IgM) react with RBCs at temperature below 37^0C, best at 0-10^0C (in extremities during cooling). Immune hemolytic anemias may be primary, without coexisting autoimmune diseases, or secondary, in association with autoimmunity. In cases of immune hemolytic anemias antibodies bind with native constituents of erythrocytes' membrane or with drug-modified proteins. The latter is described after cephalosporins, methyldopa or quinidine exposure.

Pathogenesis of immune hemolytic anemias caused by "warm" antibodies is schematically illustrated in the Fig. 1-18.

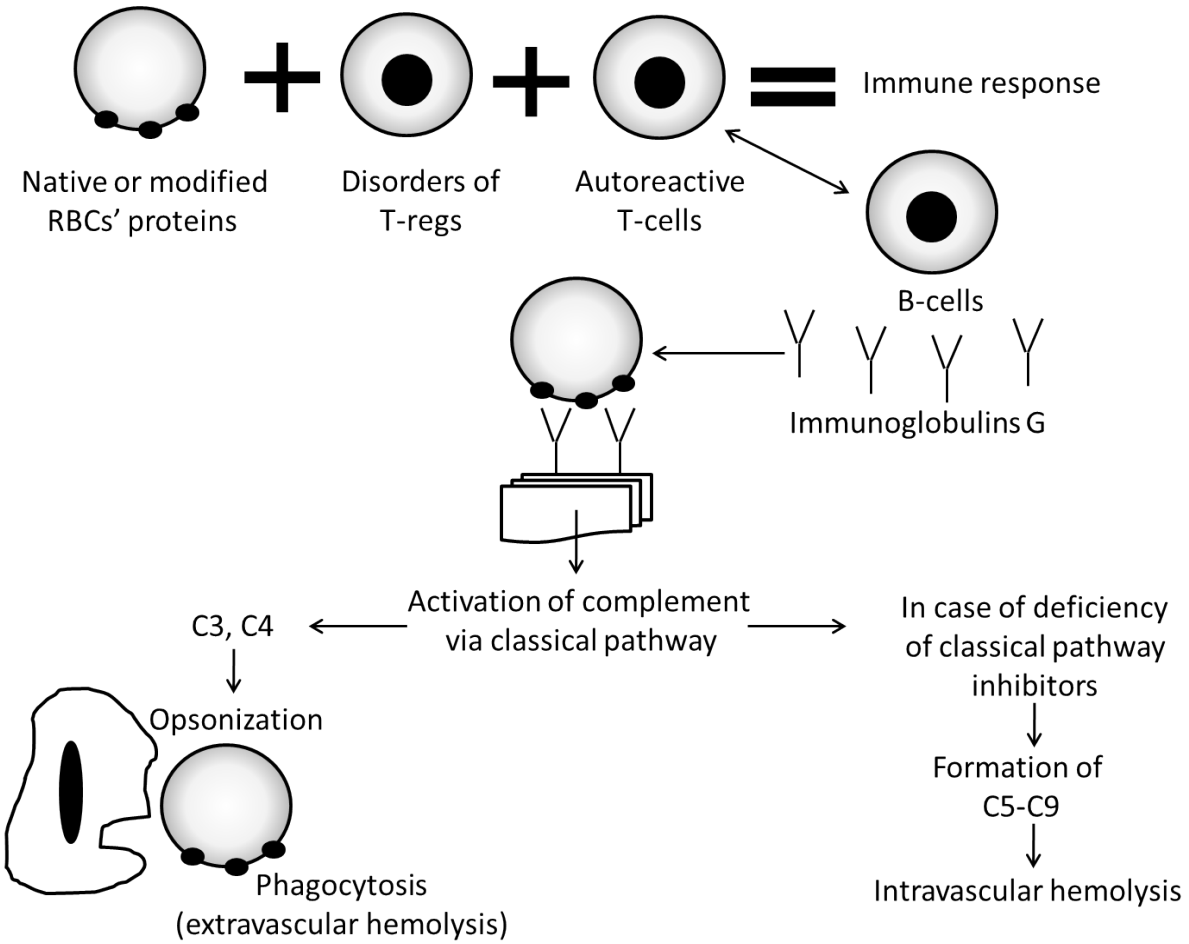


Figure 1-18. Simplified mechanisms of hemolysis caused by "warm" antibodies

This reaction is a classic example of hypersensitivity reactions of Type II. Antigens are usually fixed on the erythrocytes' membranes. Synthesis of IgG results in the formation of immune complexes. Immunoglobulins G fixed in the closed proximity on erythrocytes' membranes may serve as opsonins thus helping macrophages to recognize such RBCs with fixed immune complexes. Macrophages than destroy RBCs. Moreover, immune complexes can activate complement via classical path-

way with formation of "early" components such as C3 and C4. These components are also opsonins. Extravascular hemolysis develops in the spleen and liver. As usually, different complement regulators are located on the RBCs' membranes. They prevent formation of "late" complement products including membrane attack complex (MAC) C5-C9. Nevertheless, in case of insufficiency of complement regulators formation of MAC induces formation of pores in RBCs' membranes thus leading to osmotic lysis of erythrocytes (intravascular hemolysis).

Pathophysiologic basis for treatment of immune "warm" antibodies-mediated hemolytic anemia include: corticosteroids for the suppression of immune response; splenectomy if corticosteroids are enable to stimulate remission; immunosuppressive agents other than corticosteroids if necessary.

Autoimmune hemolysis caused by "cold" antibodies IgM includes cold agglutinins or cold hemolysins-mediated disorder. Acute form (postinfectious cold agglutinin disease) is seen in young patients with viral infections (Epstein-Barr virus) or infections caused by Mycoplasma pneumonia. It is a self-limited and mild disorder. Chronic form complicates chronic lymphocytic leukemia, B-cell lymphoma or Waldenstrom's macroglobulinemia. Most cold agglutinins react with polysaccharides on erythrocytes surface. In contrast to IgG antibodies, each IgM has 2 binding sites for C1q. The membrane inhibitor of reactive lysis stops the complement cascade before lytic components can be activated, leaving behind C3b and C4b fragments. They help phagocytic cells to coat erythrocytes with hemolysis mainly in the liver, but not in the spleen. Pathophysiologic basis for treatment of immune "cold" agglutinins-mediated hemolytic anemia include: glucocorticoids and treatment of underlying causes.

Sometimes during recovery from viral infections paroxysmal cold hemoglobinuria may develop. In this case intravascular hemolysis is resulted from "cold" hemolysins action. C1q binds to an IgG autoantibody at low temperatures. The main antigens are globoside and a glycosphingolipid. The antibody dissociates from red cells at 37° C, but C1q remains on the membrane; at the warmer temperature it triggers progression of the complement cascade to MAC with subsequent intravascular hemolysis.

Paroxysmal nocturnal hemoglobinuria is an acquired chronic hemolytic anemia characterized by persistent intravascular hemolysis, common pancytopenia and an increased risk of venous thrombosis. Intravascular hemolysis is resulted from increased susceptibility of erythrocytes to complement activation. Affected individuals have deficiency of several protective membrane proteins, for instance, CD59 and CD55. Somatic (acquired) mutation of gene encoding unique glycolipid molecule in hematopoietic cell lines, which anchors these protective proteins to the surface membrane of cells allow complement to be activated spontaneously. C5-C9 causes intravascular hemolysis. Eculizumab, a humanized monoclonal antibody against C5, which is essential for formation of the membrane attack complex, can reduce the signs of intravascular hemolysis.

Non-immune acquired hemolytic anemias are resulted from: (1) microangiopathies including disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura, hemolytic-uremic syndrome (See Fig. 1-30); (2) infections (e.g., Clostridium, malaria, babesiosis, Bartonella); (3) toxins exposure; (4) hypersplenism and fibrosis of the spleen; (5) mechanical trauma of RBCs by prosthetic materials (heart valves, ventricular or atrial septal patches, left ventricular assist devices, vascular grafts, transjugular intrahepatic portosystemic shunts); (6) exercise related trauma of RBCs in the small vessels; (7) physical or chemical-induced injury of RBCs.

Erythrocytosis

Erythrocytosis is an increase of RBCs mass. It may be (1) true and relative; (2) acquired and congenital (rare); (3) primary and secondary. True erythrocytosis is seen in patients with increased erythrocytes count when plasma volume is not diminished. Relative erythrocytosis develops in situations which are characterized by decreased plasma volume after severe diarrhea, vomiting, use of diuretics, severe burns. Increased Hct reflects dehydration but not true increase of RBCs count.

Acquired erythrocytosis develop more frequent than congenital. Example of primary acquired erythrocytosis is a myeloproliferative disorder polycythemia vera. According with mechanisms of their development, secondary acquired erythrocytosis can be classified into hypoxia-dependent and hypoxia-independent. Chronic respiratory, hypoxic, hematogenous, circulatory and combined hypoxia stimulate erythropoietin production by kidneys. EPO activates proliferative activity of the erythroid precursors in the bone marrow. Hypoxia-independent secondary erythrocytosis may be resulted from erythropoietin injections; treatment with androgens; different benign and malignant neoplasms, especially hepatocellular carcinoma or renal cell carcinoma producing EPO as a part of paraneoplastic syndrome.

Congenital erythrocytosis is a result of rare gene mutations affecting EPO or HIF signaling pathways. It may be seen also in patients with high-oxygen-affinity hemoglobinopathy, 2,3-bisphosphoglycerate deficiency and methemoglobinemia.

Uncontrolled erythrocytosis leads to secondary arterial hypertension due to increased cardiac output (CO) and systemic vascular resistance (SVR). Rise of SVR results from hyperviscosity of the blood. Disorders of microcirculation, increased risk of thrombosis and ischemic episodes are also common. The large turnover of hematopoietic cells, hyperuricemia with secondary gout due to hypermetabolism can also complicate uncontrolled erythrocytosis.

Hemochromatosis and iron overload

Hemochromatosis is a disorder of iron metabolism with clinical and laboratory signs of iron overload. It may be classified into primary (hereditary) and secondary (acquired complicated different pathologies).

Hereditary hemochromatosis with both autosomal recessive and autosomal dominant type of inheritance results from mutations of genes encoding proteins regulating iron metabolism, such as hepcidin, hemojuvelin, ferroportin, transherrin, DMT1 and different ferritin regulators.

Secondary hemochromatosis may be resulted from: (1) ineffective erythropoiesis in patients with thalassemia major, sideroblastic anemia, dyserytropoietic anemia or enzymopathies; (2) liver diseases including alcoholic liver disease, chronic hepatitis, non-alcoholic steatohepatitis and after portocaval shunt; (3) transfusions iron overload or excessive parenteral iron administration.

Elevated absorption and storage of iron result in an accumulation of ferritin, hemosyderin and melanin in the cells of parenchymatous organs. Accumulation of free redox-active iron in these organs leads to oxidative stress via Fenton reaction:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^{\cdot} + OH^{-}$$

Oxidative stress executes cellular injury with subsequent development of inflammation and fibrosis. Mechanisms of organs and tissues damage following iron overload is presented in the Table 1-11.

Table 1-11. Clinical features of excessive iron accumulation in the cells and organs during hemochromatosis

Targets	Clinical features
Liver	Accumulation of Fe^{3+} in the lysosomes of hepatocytes → liver cirrhosis, hepatocellular carcinoma
Skin	Accumulation of Fe^{3+}, hemosyderin, melanin → bronze skin pigmentation
Pancreas	Alterations of pancreatic β-cells → insulin deficiency; exocrine pancreatic insufficiency
Heart	Ferritin and hemosyderin accumulation → alteration of cardiomyocytes → cardiac fibrosis
Endocrine system	Accumulation of Fe^{3+} in the hypophysis, adrenal glands, thyroid gland and parathyroid glands with subsequent their hypofunction. Secondary hypogonadism.
Joints	Accumulation of hemosyderine in the synovial cavity and in the joint tissue → arthropathy, artritis
Macrophages	Disorders of phagocytosis. Susceptibility to *Vibrio vulnificus, Listeria monocytogenes, Yersinia enterocolitica, Salmonella enteridis, Klebsiella pneumoniae, Escherichia coli, Rhizopus arrhizus*

Pathophysiological basis for the treatment of iron overload: (1) therapeutic phlebotomy; (2) iron chelation therapy.

2. WHITE BLOOD CELLS DISORDERS

Normally, human blood contains 4.0 – 9.0×10^9/L white blood cells. Of these, the granulocytes (polymorphonuclear leukocytes, PMNs) are the most numerous. Granulocytes contain granules: neutrophilic (neutrophils); granules that stain with acidic dyes (eosinophils), and basophilic (basophils). The other two cell types found normally in peripheral blood are lymphocytes, which have large round nuclei and scanty cytoplasm, and monocytes, which have abundant agranular cytoplasm and kidney-shaped nuclei. Lymphocytes and monocytes belong to agranulocytes. Leukocytic formula is represented in the Table 1-12. Leukocytes are produced in the bone marrow in response to specific growth factors.

Table 1-12. White Blood Cells in the Peripheral Blood Smear

White Blood Cells	Absolute count, ×10^9/L	Percentage, %
Promyelocytes	0	0
Myelocytes	0	0
Metamyelocytes	0	0
Band cells	0.04-0.300	1-6
Polysegmented neuthrophils	2.0-5.5	42-72
Eosinophils	0.02-0.30	0-5
Basophils	0-0.065	0-1
Lymphocytes	1.2-3.0	18-40
Monocytes	0.09-0.60	2-9
Plasma cells	0	0

In the bone marrow most granulocytes precursors are concentrated as a proliferating and storage pool. From the storage pool neutrophils entry in the blood vessels where at least half of them are adhered to the endothelial cells with adhesion molecules, some of which are synthetized in physiological conditions and remaining circulate in the blood. Under influences of chemokines, part of circulating neutrophils are recruited in the organs and tissues where they perform their main function – phagocytosis. Distribution of neutrophils in the organism is illustrated in the Fig. 1-19.

Leukopenia

Leukopenia is a decrease of WBCs count below the normal value. Neutrophils are predominant kinds of neutrophils. Let us consider causes, mechanisms and outcomes of neutropenia.

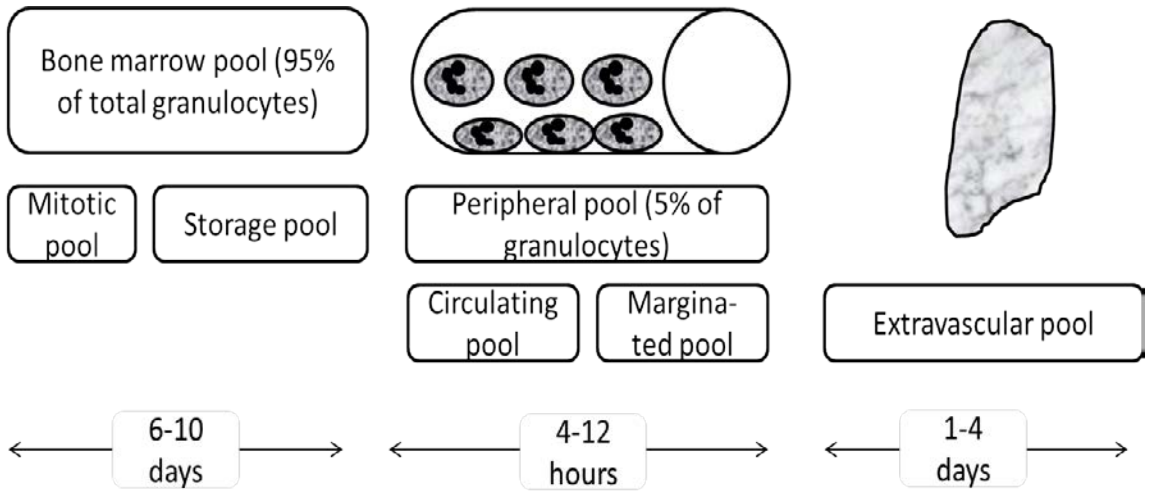


Figure 1-19. Distribution of granulocytes in the organism in physiological conditions

Causes and mechanisms of neutropenia

1. Bone marrow pool abnormalities may be hereditary (rare) and acquired (common). The latter is due to:
    - Chemicals (benzene, DDT, dinitrophenol, bismuth, arsenic, etc);
    - Drugs (cytotoxic and some non-cytotoxic, i.e. quinidine, chloramphenicol, methyldopa, captopril, ibuprofen, gold salts and others);
    - Physical factors (ionizing irradiation);
    - Immune-mediated destruction of granulocytes precursors in the bone marrow (in patients with autoimmune diseases);
    - Viral infections and infections caused by Mycobacteria strains;
    - Bone marrow replacement (by malignant cells, leukemic cells or in the case of fibrosis of the bone marrow).

The basic pathogenic event in these cases is a damage of progenitor cells in the mitotic pool of the bone marrow. As a result, the storage pool, the peripheral pool and the extravascular pool become astonished (see Fig. 1-19).

- Maturation defects. Hereditary causes of these defects are rare. Acquired causes include deficiency of vitamin B_{12}, deficiency of folates and some hematological disorders (myelodysplastic syndrome, paroxysmal nocturnal hemoglobinuria).

Maturation defects result in diminishing of storage, peripheral and extravascular pools of neutrophils.

2. Peripheral pool abnormalities may be caused by:
    - Pseudoneutropenia. This disorder is characterized by an unchanged bone marrow pool of neutrophils. The normal balance between marginated and circulating neutrophils (1:1) significantly shifts to the predomination of neutrophils adhered to the endothelial cells. It results from increased synthesis of adhesion molecules. There are two forms of pseudoneutropenia – hereditary and acquired. The first form

is usually benign. Despite the decreased neutrophil count in the peripheral blood, the extravascular pool is unchanged and no signs of immunodeficiency are seen. The second form is detected in patients with severe bacterial infections or patients with severe malnutrition or malaria. It may resolve spontaneously or after treatment.

- Intravascular sequestration in some organs. Neutrophils undergo complement-mediated agglutination in lungs or are stored in the enlarged spleen with other blood cells. Such a combination of splenomegaly, anemia, thrombocytopenia and leukopenia is termed as hypersplenism.

Intravascular sequestration of neutrophils associates with decreased peripheral pool of leukocytes.

3. Extravascular pool abnormalities. Severe bacterial, fungal or ricketsial infection or anaphylaxis leads to the shift of neutrophils from the peripheral pool in the organs and tissues, where they phagocyte pathogens.

In these cases neutrophils escape from the storage pool in the bone marrow and from the peripheral pool. This response during infections is short-term, as a rule, because with progression of inflammatory reaction, proinflammatory cytokines via colony-stimulating factors stimulate granulocytopoiesis.

Neutropenia manifests by clinical signs of secondary immunodeficiency including recurrent, often severe bacterial infections which affect skin, lungs, genitourinary system, gut and oropharynx.

Pathophysiological basis for management of neutropenia includes: (1) immunosuppressive therapy of immune-mediated causes of neutropenia (glucocorticoids, antithimocyte globuline, azathioprine); (2) recombinant human granulopoietic factors; (3) bone marrow transplantation; (4) treatment of infectious complications.

Disorders of neutrophils functions were described in the textbook “General pathophysiology: the essentials” (Part IX).

Lymphocytopenia

Lymphocytopenia is a decrease of lymphocytes count below 1.2×10^9/L. Different subsets of lymphocytes occupy heterogenous places, including lymph nodes, tonsils, spleen, bone marrow. Moreover, lymphocytes can leave and return in these organs. So sometimes it is difficult to access their real count precisely. All three groups of above-mentioned mechanisms are capable to cause lymphocytopenia. Abnormalities of lymphocytes production may be caused by ionizing irradiation, malnutrition, cytotoxic drugs, viral infections (such as measles, varicella zoster, HIV), lymphoma, adverse drug reactions and rare congenital immunodeficiencies. Abnormal lymphocytes traffic is most commonly mediated by high doses of glucocorticoids in stressfull conditions (severe acute infections, trauma, and hemorrhage), causing redistribution of these cells from peripheral compartment in the tissues. Increased destruction of lymphocytes may be immune- or non-immune mediated. First is common in patients with autoimmune disorders; second occurs in pa-

tients with loss of lymph via thoracic duct fistulas, in patients with protein-losing enteropathies or in patients with congestive heart failure.

Leukocytosis

Leukocytosis is an increase of total WBCs above 9.0×10^9/L. Depending on type of WBCs, whose count is predominate, leukocytosis can be classified into neutrophilic, eosinophilic, basophilic, lymphocytosis and monocytosis (Table 1-13).

Table 1-13. Characteristic of different types of leukocytosis

Type of leukocytosis	Definition	Common causes of leukocytosis
Neutrophilic (neutrophilia)	Increase of absolute neutrophil count more than 5.5×10^9/L or more than 72%	Infections, rheumatic and autoimmune diseases, neoplasms, poisoning, trauma, tissue necrosis, hypoxia, ketoacidosis, lactic acidosis, thyrothoxicosis, acute hemolytic anemias, recovery from bone marrow failure, drugs (corticosteroid, lithium salts, epinephrine, granulocyte colony-stimulating factor).
Eosinophilic (eosinophilia)	Increase of absolute eosinophil count more than 0.3×10^9/L or more than 5%	Atopic and allergic diseases, parasitic (especially helminthic) infections, fungal infections, leukemia or tumor-associated eosinophilia, some pulmonary and gastrointestinal diseases, specific immune deficiencies, hypoadrenalism
Basophilic (basophilia)	Increase of absolute basophil count more than 0.065×10^9/L or more than 1%	Allergic disorders, inflammatory diseases (juvenile rheumatoid arthritis, ulcerative colitis), viral infections, tuberculosis, severe hypothyroidism, malignancies (lymphomas, different solid tumors, leukemias) and drug-induced (prolonged use of estrogen-containing drugs).
Lymphocytosis	Increase of absolute lymphocyte count more than 3.0×10^9/L or more than 40%	Infections (infectious mononucleosis, pertussis, many viral infections, toxoplasmosis, brucellosis, typhoid), acute and chronic lymphocytic leukemia, lymphoma, neoplasms, Grave's disease, drug reaction (tetracycline).
Monocytosis	Increase of absolute monocyte count more than 0.6×10^9/L or more than 9%	Infections (tuberculosis, brucellosis, typhoid and paratyphoid, fungal infections, syphilis, viral infections, protozoa), neoplasms, leukemias, myeloma, ulcerative colitis, cirrhosis, drug reactions, recovery from bone marrow suppression.

Neutrophilia results from:

(1) Releasing of neutrophils from the storage pool in the bone marrow through the action of granulopoietic factors during infections and inflammation.

Such mechanism can be mediated by proinflammatory cytokines. Expansion of both peripheral pool and extravascular pool is seen (Fig. 1-19).

(2) Demargination of adhered neutrophils, with the changing of the ratio between marginated and circulating neutrophils in the peripheral pool. Demargination is mediated via cortisol and epinephrine action. Cortisol, whose concentration rises during inflammation, stimulates detachment of neutrophils from endothelial cells. This knowledge helps to understand, why a patient should undergo blood tests in the morning, before food intake, in quite atmosphere.

(3) Stimulation of mitotic pool in the bone marrow during late phase of inflammation, mediated by hematopoietic factors stimulated in turn by proinflammatory cytokines. Bone marrow pool, peripheral and extravascular pools are extended (Fig. 1-19).

Neutrophilic leukocytosis is often accompanied with toxic granulation, presence of vacuoles in the cytoplasm and presence of Döhle bodies in neutrophils (Fig. 1-20, Supplement). Toxic granules are dark, coarse inclusions which appear during bacterial infections. Vacuoles can be found during severe, poorly regulated inflammation, including sepsis. Döhle bodies are small patches in the cytoplasm, which can be detected in neutrophils during bacterial infections.

Neutrophilic leukocytosis may coexist with **"shift to left"**. To better understand the phenomenon, it is useful to recall stages of granulocytes formation and differentiation (Fig. 1-21).

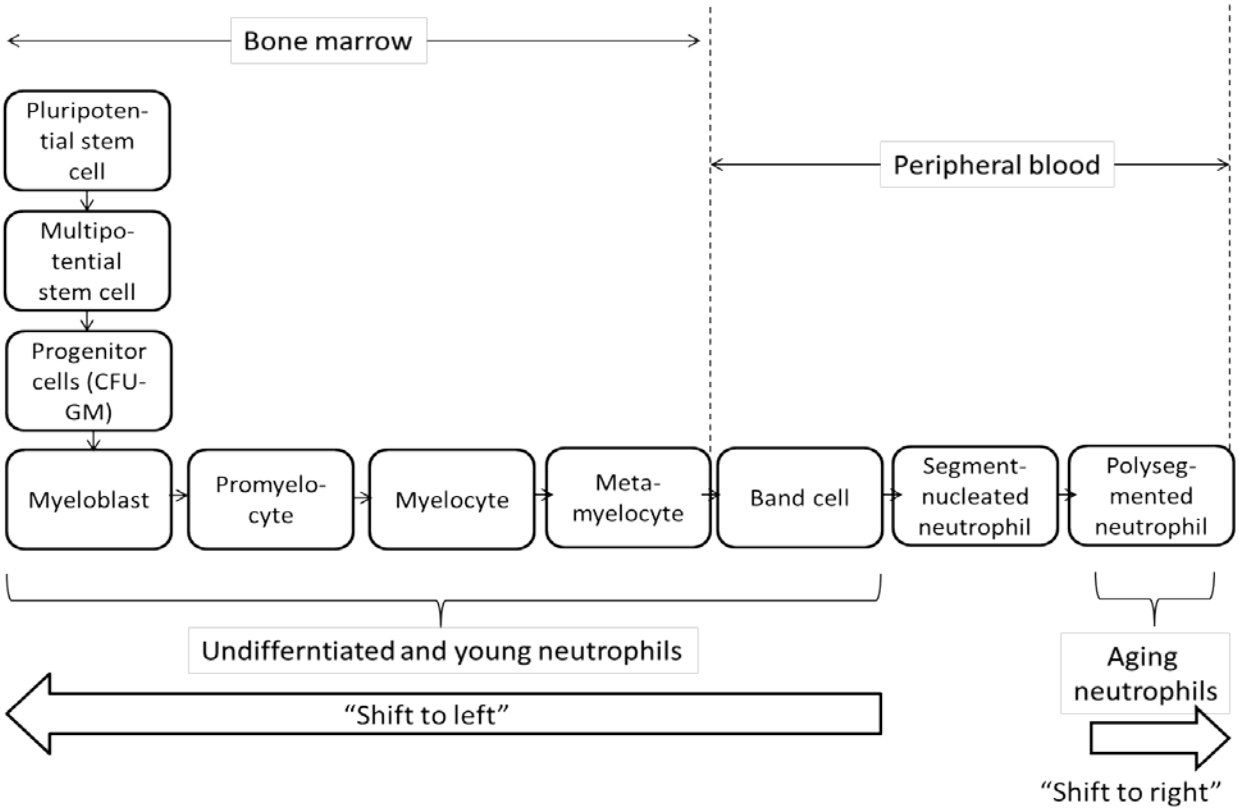


Figure 1-21. "Shift to left" and "shift to right"

CFU-GM, Colony Forming Units for Granulocytes and Monocytes

"Shift to left" is characterized by an increase count of band cells, metamyelocytes, sometimes myelocytes and even myeloblasts. It may develop during severe infections, necrosis or in leukemia. **"Shift to right"** is a phenomenon in which number of polysegmented neutrophils (with lobe more than 5, usually 7-9 in the nucleus) rises. It reflects "aging" of granulopoietic germ in patients with megaloblastic anemia and rarely – with leukemias.

Leukemoid reactions

Inflammation accompanied with leukocytosis, in which total WBCs count does not exceed 30.0×10^9/L usually. Excessive leukocytosis ($30.0\text{-}50.0\times10^9$/L) or leukemia-like changes in the formula at normal or even low total WBCs' count in a patient who doesn't suffer from leukemia is termed as a leukemoid reaction. It reflects an excessive response of the healthy bone marrow to different cytokines, which are produced by different cells during severe trauma or infections.

Depending on the type of leukocytes, whose count increases, leukemoid reactions can be classified into myeloid and lymphoid. Lymphoid leukemoid reactions are most common; they may develop in patients with viral infections, some bacterial infections (see Table 1-13) and in patients with malignancies as a manifestation of paraneoplastic syndrome. Different cytokines stimulate growth of different subsets of lymphocytes: IL-2, 3, 7 and 15 induce expansion of T-lymphocytes; IL-1, 2 and 12 stimulates development of NK-cells, whereas IL-4, 5, 6, 7, 10, 13, 14 and 15 are responsible for the expansion of B-lymphocytes.

Myeloid leukemoid reactions may develop in situations which were discussed in the Table 1-13. They also combine with "shift to left" and toxic inclusions in granulocytes.

Peripheral blood smear in patient with leukemoid reaction often remind such during corresponding (lymphoid or myeloid leukemia). To differentiate these leukemia-like hematological changes, it is necessary to carefully analyze the underlying disease, perform cytogenetic analysis or investigate aspirate of the bone marrow. Adequate treatment of underlying cause of leukemoid reaction will result in normalization of peripheral blood smear with time.

Leukemias

Leukemias are malignant neoplasms of hematopoietic cells characterized by diffuse replacement of the bone marrow by these neoplastic cells. For better understanding of etiology and pathogenesis of leukemia, it is strongly recommended to revise material stated in the Part XV "Tumor growth" (in the textbook "General pathophysiology: the essentials").

Leukemias are classified into acute and chronic (Table 1-14); myeloid and lymphoid. Acute leukemias may be classified into acute myeloblastic leukemia and acute lymphoblastic leukemia.

Table 1-14. Comparison of acute and chronic leukemias

Features	Acute leukemia	Chronic leukemia
Cellular origin	Hematopoietic precursors are arrested in the early stage of development (blasts)	More differentiated precursors
Degree of cellular differentiation	Low	Higher
Age of onset	Early in the life, more common in children	Adult and aged persons
Clinical outcome	Explosive progression and death without treatment	More slow progression, may transform from chronic to accelerated stage. Blast crisis is common complication
Blast's content in the bone marrow smear	>30	<10; blasts increase in blast crisis and appear in the peripheral blood

According with French-American-British (FAB) classification, **acute myeloblastic leukemia** has several subtypes:

M0 – acute undifferentiated leukemia;
M1 – acute myeloid leukemia with minimal differentiation;
M2 – acute myeloid leukemia with differentiation;
M3 – acute promyelocytic leukemia;
M4 – acute myelomonocytic leukemia;
M5 – acute monocytic leukemia;
M6 – acute erythroleukemia;
M7 – acute megakaryocytic leukemia.

↓ Increase of degree of differentiation of myeloid leukemic cells

} Leukemic cells belong to monocytic lineage

} Leukemic cells belong to erythroid cell lineage

} Leukemic cells belong to precursors of platelets

Acute lymphoblastic leukemias according with FAB classification are subdivided into:

L1 – acute lymphoid leukemia, childhood variant;
L2 – acute lymphoid leukemia, adult variant;
L3 – acute lymphoid leukemia, Burkitt-like variant.

World Health Organization classification of acute leukemias, besides above mentioned principles, together with cytogenetic and molecular findings, is more complex.

Peripheral blood smear in patients with acute leukemia is characterized by changes of WBCs count ranging from severe leukocytosis in advanced stage (more than 80.0×10^9/L) to normal or even leukopenia, anemia and thrombocytopenia. Blasts can be detected in the peripheral blood. They look as cells with diameter 10-18 μm, large round or oval nucleus and scanty, blue and agranular cytoplasm (Fig. 1-22 and 1-23, Supplement).

It is difficult to distinguish myeloblast from lymphoblast under light microscopy. Bone marrow aspiration, cytochemical staining and immunophenotyping help differentiate the type of acute leukemia. For instance, leukemic lymphoblasts are focal positive for acid phosphatase, whereas myeloblasts are positive for sudan black. M0 myeloblasts are negative to myeloperoxidase, but more differentiated leukemic myeloid cells react positively to myeloperoxidase. During immunophenotyping it is possible to detect CD13, CD14, CD 33 and CD 34 on the surface of myeloblasts. At least 60% of leukemic lymphoblasts express cell surface glycoprotein CD10. Most common cytogenetic abnormalities during acute lymphoblastic leukemia are a gain of 8 chromosome, or loss of part or all of 7 or 5 chromosome. In adults with acute lymphoblastic leukemia Philadelphia chromosome is common (see Part XV "Tumor growth" in the textbook "General pathophysiology: the essentials").

In the leukogram of patients with acute myeloblastic leukemia, hiatus leukemicus may be detected. It is characterized by the presence of myeloblasts in the peripheral blood smear, absence of intermediate forms of granulocytes and appearance of more differentiated granulocytes. This phenomenon reflects block in differentiation of leukemic cells.

Essentially, chronic leukemias are subdivided into most common chronic myeloid (synonyms are: myelogenous, myelocytic, granulocytic) and chronic lymphocytic leukemia. Other less common forms are also described.

Chronic lymphoid leukemia is resulted from accumulation of lymphocytes, most commonly B-lymphocytes and less common T-lymphocytes in the bone marrow, lymph nodes, spleen, liver and other organs. Total WBCs count increases with development of lymphocytosis. Atypical lymphocytes are larger than normal lymphocytes. Gumprecht shadows or "smudge cells" can be detected in the peripheral blood. These are crushed leukemic lymphocytes; however, they are not specific for lymphocytic leukemia (Fig. 1-24, Supplement).

Chronic myeloid leukemia is characterized by overproduction of granulocytes with marked total WBCs count elevation. Other granulocytes at different stages of their maturation are detected in the peripheral blood (Fig. 1-25). Myeloblasts in the peripheral blood rarely exceed more than 10%. Basophilia and eosinophilia may coexist. Thrombocytopenia or thrombocytosis can be detected. Most common cytogenetic abnormality is Philadelphia chromosome in the leukemic cells. Blast crisis may develop in one third of patients with chronic myeloid leukemia. It results from acceleration of genomic instability of leukemic cells and gain of refractoriness to chemotherapeutic drugs. Chronic myeloid leukemia belongs to the group of myeloproliferative neoplasms. These groups also include polycythemia vera, essential thrombocytemia (see later) and others.

Polycythemia vera

Polycythemia vera (primary polycythemia) is a myeloproliferative neoplasm, which is characterized by abnormal proliferation of myeloid elements with erythrocytosis, leukocytosis and thrombocytosis. Level of erythropoietin in the

blood in patients with polycythemia is not elevated, in contrast to secondary erythrocytosis. Peripheral blood test reveals increase of hemoglobin concentration above the normal, erythrocytosis, rise in Hct, leukocytosis and thrombocytosis. Splenomegaly is common. Patients with polycythemia vera often suffer from arterial hypertension (due to polycythemic hypervolumia and increase of systemic vascular resistance resulted from hyperviscosity); pruritus, especially after bathing, erythromelalgia (acral dysesthesia and erythema) and thrombosis.

Essential thrombocytosis (primary thrombocythemia)

This myeloproliferative disorder is characterized by abnormal expansion of myeloid cells – precursors of megakaryocytes. Increased platelets count in the peripheral blood associates with their functional disorders. Essential thrombocytosis often complicates by venous or arterial thrombosis and bleeding disorders due to functional abnormalities of platelets. One should differentiate primary thrombocytosis from secondary (reactive) thrombocytosis caused by infections, trauma, hemorrhage, severe iron deficiency, some malignancies and some autoimmune diseases. Splenectomy also may lead to reactive thrombocytosis. Bone marrow investigation helps to distinguish these types of thrombocytosis.

Different leukemias may have common hematological and clinical findings (Table 1-15):

Table 1-15. Pathogenesis of hematological and clinical syndromes during leukemias

Syndromes	Description, mechanisms of development
Anemia	1. Decrease production of RBCs due to: replacement of RBCs precursors by tumor cells; iron deficiency and hypoproteinemia due to anorexia; decrease of erythropoietin synthesis in response to cytokines; side effects of chemotherapy. 2. Immune- and non-immune mediated hemolysis (extravascular and intravascular).
Fever and intoxication	1. Secondary immunodeficiency as a result of poor differentiation and functional defects of lymphocytes with increased susceptibility to infections. 2. Increased turnover of neoplastic cells with rise of concentration of proinflammatory cytokines (secondary pyrogens) from destroyed leukemic cells.
Hyperplastic syndrome	Characterized by splenomegaly, hepatomegaly, lymphoadenopathy, and tenderness of bones. Caused by: 1. Loss of contacts between leukemic cells and bone marrow stroma. 2. Replacement of lymphoid tissues and organs by leukemic cells. 3. Immune response to the tumor antigens in the lymph

	nodes. 4. Destruction of leukemic cells by cytotoxic T-lymphocytes within lymph nodes.
Disseminated intravascular coagulation	1. Releasing of prothrombotic factors from the leukemic cells (tissue factor, microparticles, plasminogen activators inhibitors, Factor V receptors, adhesion molecules) with formation of thrombin and fibrin. 2. Endothelial dysfunction with loss of athrombogenic surface, activation of platelets and leukocytes by proinflammatory cytokines. 3. Hyperviscosity of the blood (caused by immunoglobulins, severe leukocytosis, eryhtrocytosis in polycythemia vera, and thrombocytosis. 4. Co-existing thrombophilia (hereditary, if it has developed before leukemia, and/or acquired due to surgery, immobilization or side effects of chemotherapy). Characterized by thromboembolic complications, in the late stage – by bleeding.
Hemorrhagic syndrome	1. Thrombocytopenia caused by replacement of normal bone marrow by leukemic cells. 2. Damage of vascular wall. 3. Consumption of clotting factors, thrombocytopenia and activation of fibrinolysis following late stage of disseminated intravascular coagulation.
Immune deficiency	Characterized by infectious complications, necrotic lesions resulted from abnormal functions of leukocytes.
Leukostasis syndrome	Develops in case severe leukocytosis, when WBCs count more than 100×10^9/L. Capillary stasis → sludge phenomenon → hypoxia (in the pulmonary capillaries it may result in hypoxemia, in the brain capillaries – in unconsciousness).
Neuroleukemia	Characterized by symptoms of leptomeningithis due to: 1. Infiltration of the meninx by the leukemic cells. 2. Leukostasis. 3. Hypoxia and inflammation.
Jaundice	1. Increased RBCs hemolysis. 2. Damage of hepatocytes by chemotherapeutic agents.
"Tumor lysis" syndrome	Massive and abrupt lysis of malignant cells caused by chemotherapy results in releasing of cellular components in the blood (anions, cations, metabolic products of proteins, nucleic acids) with subsequent metabolic disorders. They include: hyperuricemia with development of nephropathy and acute renal failure; disorders of sodium, potassium and calcium balance.

Pathophysiological basis for the treatment of leukemia: chemotherapy, bone marrow transplantation, prophylaxis and treatment of complications, radiotherapy in case of chronic lymphoid leukemia. New strategies are used for treatment of leukemia (see Table 15-2, Part XV "Tumor growth" in the textbook "General pathophysiology: the essentials").

Lymphomas

Lymphomas are malignant solid tumors of lymphoreticular origin. To better understand their cellular substrate, it is useful to show briefly the steps of lymphocytes formation and maturation. Bone marrow-derived lymphoid stem cells differentiate into T-cell precursors and B-cell precursors. After that T-precursors transform into naïve T-cells in the thymus. After going out from the thymus, naïve T-cells occupy lymph nodes and proliferate to T-effectors after antigenic stimulation. B-cell precursors differentiate in the bone marrow into naïve B-cells. Naïve B-cells settle lymph nodes, where they differentiate (in the mantle and marginal zones of lymph nodes paracortex). In the medulla of lymph nodes, B-cells transform in Ig-producing plasma cells. Lymphomas are derived from mutated lymphocytes (T- or B-cells), histiocytes and their precursors.

Lymphomas are classified into non-Hodgkin's lymphomas, which are most common, and Hodgkin's lymphomas. The hallmarks of Hodgkin's lymphomas are presence of Reed-Sternberg cells which belong to cells of lymphoid origin. These large popcorn-like cells have bilobed or lobulated nuclei and express CD15, CD30 or CD20. Non-Hodgkin's lymphomas are most frequent than Hodgkin's lymphomas. There are lot of classifications of lymphomas, including the newest WHO.

Lymphomas are multifactorial diseases. Infections (especially viral, caused by Epstein-Barr virus, HIV; bacterial – Helicobacter Pylori); ionizing irradiation, some chemicals and drugs; genetic abnormalities may cause clonal proliferation of immune cells. Lymphomas are characterized by lymphadenopathy, splenomegaly, liver enlargement, intoxication syndrome, hematologic abnormalities (anemia, changes of WBCs count, thrombocytopenia or thrombocytosis, elevation of ESR) and immunologic abnormalities.

Pathophysiological basis for the treatment of lymphomas: cutaneous radiation therapy in early stages of disease in patients with superficial lymphoadenopathy and skin involvement; chemotherapy, allogenic stem cell transplantation, prophylaxis and treatment of complications.

Plasma cell disorders

Plasma cell disorders are neoplastic or potentially neoplastic diseases characterized by clonal proliferation of immunoglobulin-secreting plasma cells which are derived from B-cells. Normal immunoglobulins consist of two identical heavy polypeptide chains (α, γ, μ, ε or δ for IgA, IgG, IgM, IgE or IgD, respectively) and two light chains (κ, λ). In the most clonal plasma cell disorders, intact immunoglobulins are secreted as an electrophoretically and immunologically homogeneous (monoclonal) M-protein. In some cases heavy chain expression is lost and only

monoclonal light chains of immunoglobulins are secreted. These light chains were termed as Bence-Jones proteins. They are excreted in the urine. When light chain expression is lost in extremely rare situations, only heavy chains are secreted.

Plasma cell disorders include:

- Premalignant monoclonal gammopathies;
- Multiple myeloma and related malignancies (IgG, IgA, IgD, IgE and free light-chains);
- Waldenström's macroglobulinemia (IgM);
- Heavy chain disease;
- Cryoglobulinemia;
- Immunoglobulin light chaim amyloidosis.

Pathophysiological characteristic of multiple myeloma. Multiple myeloma is a neoplastic disorder affecting plasma cells with poor identified etiology. Physical and chemical carcinogens may lead to different cytogenetic abnormalities in the clone of plasma cells with their hyperresponsiveness to growth factor and accelerated neoangiogenesis. Multiple myeloma evolves from monoclonal gammopathies of undetermined significance. Mechanisms of syndromes observed in multiple myeloma are presented in the Table 1-16.

Table 1-16. Syndromes which are common in multiple myeloma

Syndrome	Mechanisms of development
Lytic bone lesions	The normal bone marrow is replaced by reddish-gray tumors. Most common affected bones are skull, ribs, spine, pelvis, further – limbs. Malignant cells stimulate osteolysis via (1) activation of osteoclasts; (2) suppression of osteoblasts differentiation and activity. These mechanisms are resulted from increased RANKL/osteoprotegerin ratio. RANK (receptor activator of NF-κB) has its ligand (RANKL). RANKL has also decoy ligand – osteoptrotegerin. In myeloma level of RANKL on osteoblasts increases, whereas level of osteoprotegerin reduces. Abnormal RANKL/osteoprotegerin ratio results in accelerated bone resorption with bone pain and pathological fractures.
Renal failure	Results from: (1) light chain casts nephropathy and obstruction of distal and collecting tubules; (2) hypercalcemia and hyperuricemia.
Immunodeficiency	Caused by neutropenia and deficiency of normal immunoglobulins.
Anemia	Related to replacement of bone marrow by neoplastic cells and abnormal response to erythropoietin.
Hyperviscosity syndrome, ↑↑ ESR	Caused by hyperimmunoglobulinemia, results in disorders of microcirculation and is characterized by headache, visual disturbances, ischemic episodes.

Disorders of hemostasis	Bleeding disorders are resulted from thrombocytopenia and/or functional disorders of platelets; increased risk of thromboembolic complications due to hyperviscosity.
Neurologic symptoms	Radiculopathy due to compression of nerves by vertebral injury; peripheral neuropathy related to amyloidosis.

Pathophysiological basis for treatment of multiple myeloma: despite chemotherapy with alkylating drugs and supportive care the median survival after diagnosis is not exceeds 2 years. Autologous stem cell transplantation may have a good result.

3. BLEEDING DISORDERS

Bleeding disorders (hemorrhagic diathesis) are characterized by a tendency of excessive spontaneous bleeding or severe bleeding after trauma or surgery. To better understand the principles of hemostasis investigation, classification of bleeding disorders and their pathogenesis, it is absolutely important to recall basic notions about primary and secondary hemostasis (Textbook "General pathophysiology: the essentials", Part VIII).

Based on the main mechanism, all bleeding disorders can be classified as follows:

I. Bleeding disorders resulted from predominant disorders in primary hemostasis:
   A. Caused by decreased platelet count (thrombocytopenia);
   B. Resulted from impaired platelet functions (thrombocytopathia);
   C. Due to injury of vascular wall.
II. Bleeding disorders related to principal impairment of secondary hemostasis:
   A. Caused by decreased concentration of clotting factors in the blood;
   B. Caused by abnormal activity of clotting factors.
III. Bleeding disorders resulted from excessive fibrinolysis.
IV. Combined disorders.

According with natural history, all bleeding disorders can be classified on hereditary and acquired.

Bleeding disorders resulted from impairment of primary hemostasis

To better understand the pathogenesis and clinical signs of such disorders, it is necessary to discuss principles of investigation of primary hemostasis. For instance, bleeding time is measured with an incision or a prick of forearm, or finger, or earlobe depending on chosen method. This parameter reflects capillary function during capillary bleeding and the ability of platelets to form a platelet plug. Depending on the method, bleeding time may vary in normal individuals from 2 to 8 minutes. Prolonged bleeding time may be due to: (1) vascular abnormalities; (2) decreased platelet count (thrombocytopenia); (3) impaired platelet functions (thrombocytopathia); (4) severe deficiency of factor V or factor IX.

Peripheral blood platelet count helps to verify or rule out of thrombocytopenia. Normal platelet count assessed automatically is $180.0\text{-}320.0\times10^9$/L. Decrease in platelets count less than 100.0×10^9/L is determined as thrombocytopenia. **Thrombocytopenia**, or decreased platelets count, may be mild (platelets count $50.0\text{-}100.0\times10^9$/L) or severe (platelets count less than 50.0×10^9/L). Mild thrombocytopenia is displayed by bleeding from mucous membranes and superficial cutaneous bleeding (petechiae, purpura) after surgery or trauma. Severe thrombocytopenia leads to spontaneous bleeding.

Thrombocytopenia may be hereditary (rare) and acquired. Causes and mechanisms of thrombocytopenia are presented in the Table 1-17.

Table 1-17. Etiology of thrombocytopenia

Basic mechanism of thrombocytopenia	Causes of thrombocytopenia
Hypoplasia of hematopoietic stem cells	Hereditary: Wiskott-Aldrich syndrome, May-Hegglin anomaly, thrombocytopenia with absence of radii syndrome Acquired: aplastic anemia; drug-, chemical-, radiation-, infection-induced (HIV, for instance) damage of the bone marrow
Replacement of normal bone marrow	Infiltration of bone marrow by leukemic cells or metastatic cells, replacement of normal bone marrow by connective tissue (myelofibrosis)
Ineffective thrombocytopoiesis	Vitamin B_{12} or folates deficiency, hematopoietic dysplastic syndrome
Increased destruction of platelets	Immune: idiopathic thrombocytopenic purpura, cancer, some drugs, autoimmune diseases Non-immune: disseminated intravascular coagulation, hemangioma, thrombotic thrombocytopenic purpura, malaria, sepsis
Redistribution of platelets	Hypersplenism (sequestration of platelets in enlarged spleen)
Dilutional thrombocytepenia	Excessive transfusion of fluids, plasma or old blood

Let us consider immune and non-immune thrombocytopenia.

Idiopathic thrombocytopenic purpura (ITP) is an example of an autoimmune disease. It may be acute or chronic; primary (without underlying autoimmune disorders) or secondary (associated with autoimmune diseases). T-cells become activated after recognition of platelet autoantigens (glycoprotein receptors GP IIb/IIIa or GP Ib/IX) by antigen-presenting cells. T-cells cooperate with B-cells. Activated B-cells transform to plasma cells, producing autoantibodies (IgG) against GP IIb/IIIa or GP Ib/IX that are expressed not only on platelets but also on megakaryocytes in the bone marrow. Fc-receptors for IgG on the macrophages recognize immune complexes on the surface of platelets and macrophages phagocytize platelets in the spleen, and to a less extent, megakaryocytes in the bone marrow. Some megakaryocytes with autoantibodies against glycoprotein receptors die from excessive apoptosis in the bone marrow. Pathophysiologic basis for treatment of ITP include splenectomy, corticosteroids and immunosuppressive agents, thrombopoietin, antibodies against CD154 and antibodies against CD20, immune globulin, plasmapheresis.

Drug-induced thrombocytopenia may develop after use of quinine, quinidine, sulfonamides, gold salts and unfractionated heparin. The latter, however, associates with thrombosis, but not bleeding (See Part VIII in “General pathophysiology: the essentials”). Drugs can lead to immune-mediated thrombocytopenia by

a variety of mechanisms: (1) directly stimulating anti-platelet antibody production; (2) hapten mechanism and (3) "innocent bystander" phenomenon. Drugs may interfere with platelet surface structures (proteins), with formation of neoantigens. Activation of immune system results in the formation of platelet surface immune complexes and phagocytosis of such macrophages in the spleen. Withdrawal of such drugs leads to resolution of immune response and recovery. Acute thrombocytopenia also can be resulted from the deposition of immune complexes on the platelet surface via an "innocent bystander" phenomenon. Such antibody-coated platelets are then cleared from the circulatory system by Fc-receptor expressing macrophages in the spleen.

Thrombotic microangiopathies are examples of non-immune thrombocytopenia. Thrombotic microangiopathies include thrombocytopenic purpura (TTP), which is more common in adults, and hemolytic uremic syndrome (HUS), which is more common in children. Notable hallmarks of thrombotic microangiopathies are: microangiopathic hemolytic anemia; thrombocytopenia; compromised tissues perfusion; acute renal failure in hemolytic-uremic syndrome. Thrombotic thrombocytopenic purpura can be developed in individuals with genetic predisposition – decreased activity of the enzyme ADAMTS13. ADAMTS protease (**A** **D**isintegrin-like **A**nd **M**etalloprotease With **T**hrombo**s**pondin Type 1 Repeats) is synthetized in the liver and has half-life in the circulation from 2 to 3 days. Von Willebrand Factor (vWF), which is synthetized in endothelial cells and stored in Weibel-Palade bodies, is the only known substrate of ADAMTS13. Hereditary-based or acquired (after synthesis of antibodies against ADAMTS13) decreased activity of ADAMTS13 leads to formation of large multimeres of vWF stimulating activation and aggregation of platelets. Pathogenesis of TTP is illustrated in the Fig. 1-26.

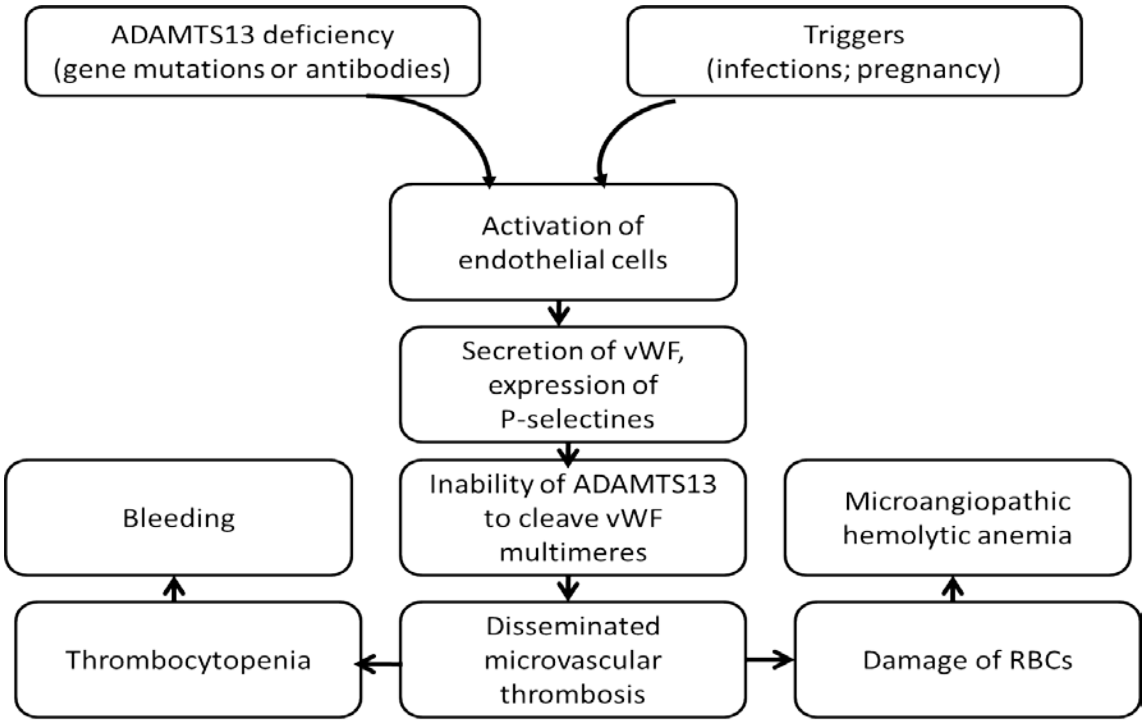


Figure 1-26. Pathogenesis of thrombotic thrombocytopenic purpura

Hemolytic-uremic syndrome develops in children with normal activity of ADAMTS13. Infections, especially Shiga toxin-producing E. coli O157:H7 are principle triggers for HUS. Toxin binds with glomerular endothelial cells in kidneys and stimulates expression of vWF multimeres with adhesion of platelets, thrombosis and damage of red blood cells with formation of helmet cells. Acute renal failure and uremia may lead to death in the absence of treatment.

Emergency treatment for thrombotic microangiopathies includes plasmapheresis, a procedure that involves removal of plasma from withdrawn blood and replacement with fresh-frozen plasma.

Bleeding complicated thrombocytopenia results from defects in gap junctions between neighboring endothelial cells in the postcapillary venules due to lack of platelet-related throphogens acting on endothelial cells.

Platelet functional disorders (thrombocytopathies) can be classified into hereditary and acquired. Hereditary thrombocytopathies include Glanzmann'z thrombastenia, Bernard-Soulier syndrome (both with autosomal-recessive type of inheritance), autosomal-dominant storage pool disease and von Willebrand disease (See further). Pathogenesis of some hereditary thrombocytopathies is depicted in the Fig. 1-27. In storage pool disease, platelets have decreased granules and/or their abnormal content resulted from abnormal maturation of megakaryocytes in the bone marrow. Deficiency in dense granules leads to inadequate secretion of ADP from activated platelets. The absence of α-granules associates with inadequate elaboration of growth factors from platelets. Storage pool disease often combines with mild thrombocytopenia and different malformations.

Acquired platelet functional disorders are seen:

- As an adverse effects of drug therapy (NSAIDs, which inhibit COX activity and impair thromboxane A_2 synthesis, see Fig. 8-6 in "General pathophysiology: the essentials"; antiplatelet drugs; β-lactam antibiotics);
- In renal failure with uremia, because uremic toxins impair platelet aggregation;
- During liver diseases, which associate with liver failure;
- In paraproteinemias (multiple myeloma and Waldenström's macroglobulinemia), resulted from impairment of platelets and fibrinogen interactions by paraproteins;
- In acquired platelet function abnormalities caused by loss of platelet storage granules after surgeries requiring cardiopulmonary bypass, hairy cell leukemia and formation of autoantibodies against platelet structures;
- In myeloproliferative disorders including essential thrombocythemia;
- In disseminated intravascular coagulation syndrome, when fibrin degradation products impair platelet function.

To detect probable thrompocytopathia it is necessary to investigate platelet functions (adhesion to the collagen, to the glass, etc.; aggregation in response to different stimulators of aggregation including ADP, collagen, epinephrine, trom-

bine; releasing of granules content); and their structure.

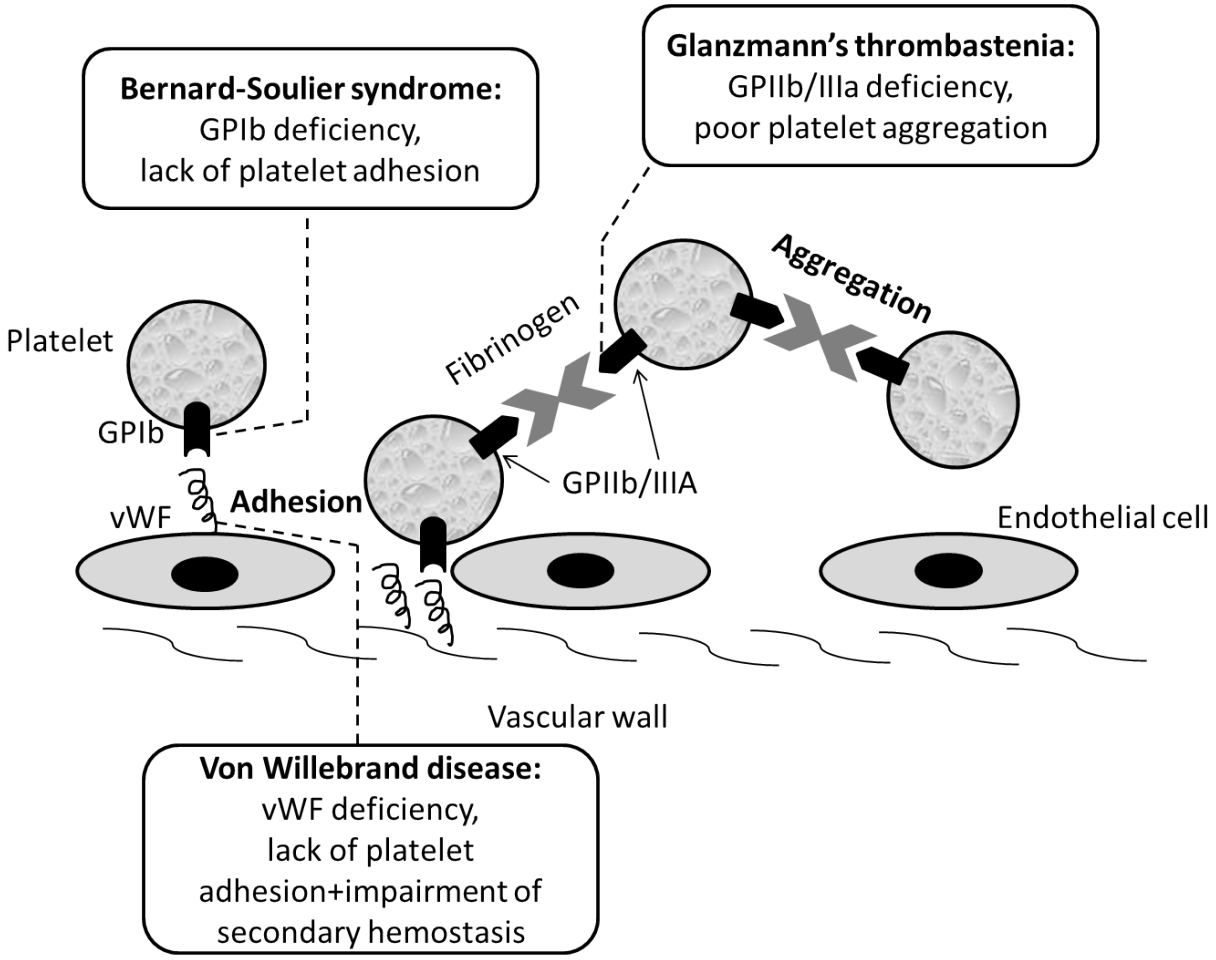


Figure 1-27. Pathogenesis of hereditary disorders of platelet function
GP, glycoproteins; vWF, von Willebrand factor

Vascular diseases may impair primary hemostasis and lead to bleeding diathesis with clinical symptoms similar those observed in platelet disorders. To reveal capillary fragility, sphygmomanometer cuff is placed to the forearm with increasing pressure in the cuff. Deflation following 5 minutes is followed by formation of superficial non-palpable cutaneous hemorrhages (petechiae). Presence of more than 20 petechiae per 3 sm^2 of the skin over the cubital fossa reflects increased capillary fragility.

Vascular diseases associated with bleeding diathesis can be subdivided into congenital and acquired. Congenital vascular diseases include hereditary hemorrhagic teleangiectasia (Rendu-Osler-Weber disease), cavernous hemangioma (Kasabach-Merritt syndrome), and connective tissue disorders (Ehlers-Danlos syndrome, osteogenesis imperfect and pseudoxanthoma elasticum). Hereditary hemorrhagic teleagiectasia, an autosomal dominant disorder, affects cardiovascular morphogenesis and vascular remodeling. Absence of subendothelial structures leads to dilation of blood vessels. Teleangiectasia affects blood vessels not only in the skin or mucous membranes but also in internal organs with increasing risk of internal bleeding. Cavernous hemangioma often combines with thrombocytopenia, due to

removal of activated platelets from circulation within hemangiomas. Hereditary-based connective tissue disorders are resulted from abnormalities in structural glycoproteins including collagen with consequent vascular fragility and weakening of the vascular wall.

Causes and mechanisms of acquired diseases of vascular wall with bleeding tendency are presented in the Table 1-18.

Table 1-18. Causes and mechanisms of acquired bleeding disorders resulted from vascular diseases

Etiology	Pathogenesis
Scurvy (severe vitamin C deficiency)	See Table 11-1 in "General pathophysiology: the essentials". Defective collagen formation in small blood vessels.
Henoch-Schönlein purpura (hemorrhagic vasculitis)	Infections, some drugs or vaccination provoke formation of immune complexes consisting of antigens and antibodies (mainly IgA). Immune complexes deposit on endothelial cells, activate complement and cause necrotizing vasculitis (hypersensitivity reaction, type III). Symmetrical purpura, abdominal pain, melena, arthralgias are common signs of disease, affecting children predominantly. Spontaneous recovery after several weeks is seen.
Amyloidosis	Alteration of normal structural support for small blood vessels and increased vascular fragility, resulted from accumulation of amyloid, leads to purpura.
Paraproteinemias (multiple myeloma and Waldenström's macroglobulinemia)	Paraproteins results in hyperviscosity, slowing of the blood flow, increase in hydrostatic pressure and vascular fragility with purpura.
Exposure of excessive concentration of glucocorticoids (Cushing's disease, Cushing's syndrome, glucocorticoid therapy)	Impairment of collagen synthesis in the vascular wall and perivascular matrix, loss of normal vascular elasticity with increased bruising, especially in the extremities.

Bleeding disorders resulted from impairment of secondary hemostasis

The most important reference tests for the assessment of secondary hemostasis are prothrombin time (PT) test and activated partial thromboplastin time (APT) test (Fig. 1-28). These tests measure time for fibrin clot formation. A prolonged PT reflects hypocoagulation and possible deficiency of VII, X, V, II or I coagulation factors. Because of reagents containing tissue factor may differ, the standardized indicator – **I**nternational **N**ormalized **R**atio (INR) is used.

$$INR = (\text{Patient's PT/reference PT})^{ISI},$$

where ISI is International Sensitivity Index, which is an experimentally obtained

value for every reagent-instrument combination in use. Normal INR is 0.85-1.35; its value below 0.85 reflects hypercoagulation, above 1.35 – hypocoagulation.

An increased APT reflects hypocoagulation from possible deficiency of VIII, IX, XI, XII, X, V, II, I coagulation factors.

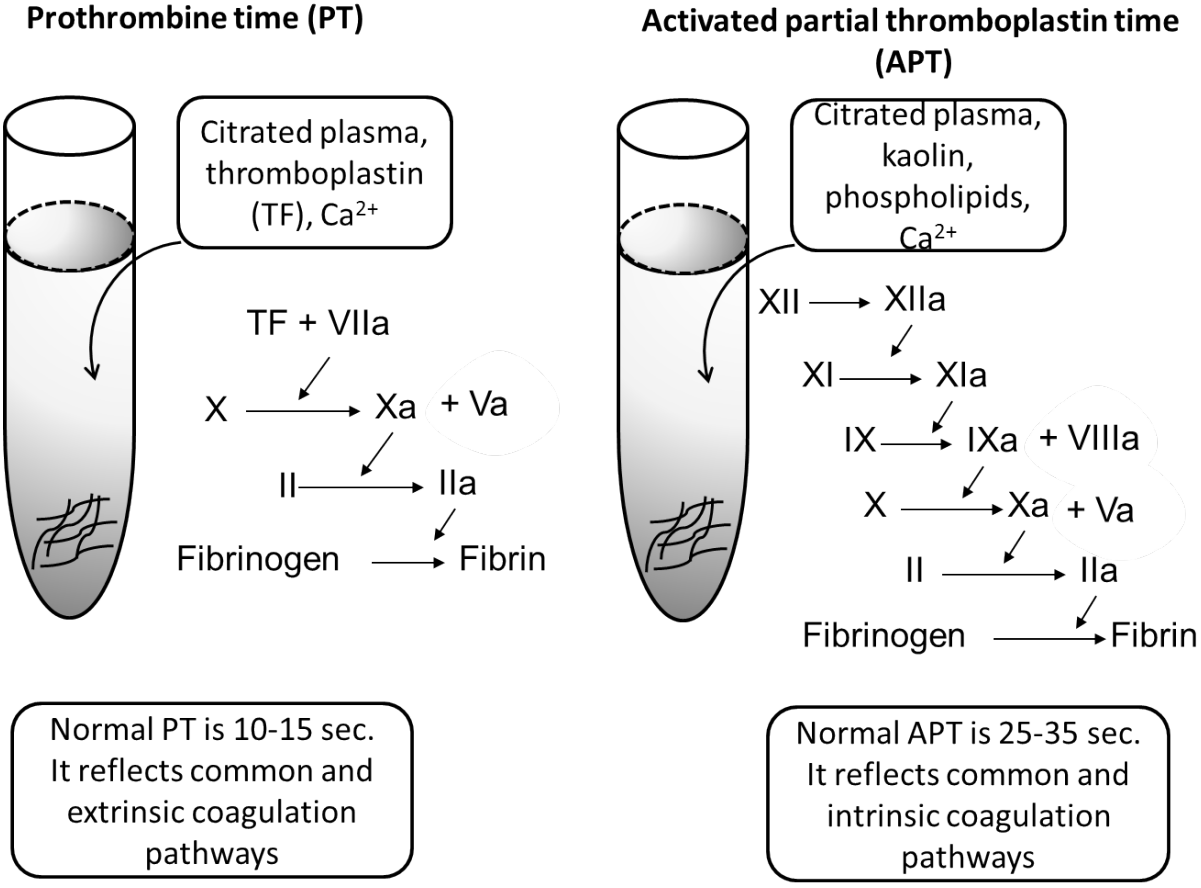


Figure 1-28. Prothrombin time and activated partial tromboplastine time tests
TF, tissue factor

Both PT and APT are screening tests, and specialized tests are necessary to diagnose different disorders of coagulation. These include determination of concentration of definite coagulation factors, antibodies against these factors, concentration of anticoagulants, components of fibrinolytic system and fibrin degradation products.

Coagulation disorders may be hereditary and acquired. Incidence of different hereditary coagulopathies is represented in the Table 1-19.

Table 1-19. Pathophysiologic characteristic of prevailing hereditary coagulopathies

Pathologies	Incidence in general population	Type of inheritance	Basic pathophysiologic mechanism
FVIII deficiency (Hemophilia A)	1:10 000	X-linked recessive	Abnormalities in intrinsic pathway lead to impaired pro-

			thrombinase formation
FIX deficiency (Hemophilia B, Christmas disease)	1:60 000	X-linked recessive	Abnormalities in contact activation of coagulation and intrinsic pathway lead to impaired prothrombinase formation
FVII deficiency	1:500 000	Autosomal-recessive (13 chromosome is involved)	Abnormalities in extrinsic pathway result in impaired prothrombinase formation
FXI deficiency (Hemophilia C, Rosenthal syndrome)	1:1 000 000	Autosomal-recessive (4 chromosome is involved)	Abnormalities in contact activation of coagulation and intrinsic pathway with subsequent impairment of prothrombinase formation
Fibrinogen deficiency	1:1 000 000	Autosomal-recessive (4 chromosome is involved)	Fibrin formation is impaired
FXIII deficiency	1:1 000 000	Autosomal-recessive (6 or 1 chromosomes are involved)	Disorders of fibrin stabilization, poor wound healing and poor scar formation
Prothrombin deficiency	1:2 000 000	Autosomal-recessive (11 chromosome is involved)	Thrombin formation is impaired

Severe hereditary coagulopathies start shortly after birth. Deep bleeding in soft tissues (hematoma) and in joints after trauma and surgery is common. Mild and moderate hereditary coagulopathies may be clinically silent until they are detected with abnormal coagulation tests. Treatment and prevention of bleeding in patients with hereditary coagulopathies require replacement of a deficient clotting factor. Gene therapy of hemophilias is in development now.

Von Willebrand disease is an example of a hereditary disorder with both impaired primary and secondary hemostasis, resulted from quantitative or qualitative von Willebrand factor (vWF) deficiency. The factor is produced in endothelial cells and stored in Weibel-Palade bodies; after polymerization large multimeric complexes of vWF appear on the surface of endothelial cells. In less amounts, vWF are produced by megakaryocytes in the bone marrow. Polymerization of vWF is a critical step for its subsequent hemostatic activity. After endothelial damage activated by shear forces, vWF participates in platelets adhesion to damaged vascular wall (via GPIb-IX and binding with collagen). Moreover, vWF binds

to factor VIII and protects it from premature degradation. That is why mild forms of von Willebrand disease manifest clinically by bleeding from mucous membranes, whereas severe forms cause serious hemophilia-like bleeding. There are three main types of von Willebrand disease:

- Type 1 is a quantitative defect of vWF with a decreased level of factor, which is normally structured. The level of FVIII can be decreased as well. Degree of disease is mild or moderate.
- Type 2 involves about 20 subtypes of von Willebrand disease with qualitative defects of vWF. Concentration of FVIII may be normal or decreased.
- Type 3 is characterized by absence or very low plasma concentration of vWF. FVIII concentration is also very low.

Pathophysiologic basis for treatment of von Willebrand disease: (1) stimulation of releasing of vWF from endothelial cells with analog of antidiuretic hormone – desmopressin in type 1 of the disease; (2) infusion of vWF and/or FVIII concentrate; (3) antifibrinolytic agents (ε-aminocapronic acid, tranexamic acid).

FXII deficiency is a rare hereditary disorder with no clinical picture of bleeding. 8-10% of affected individuals may have increased risk of thrombosis due to impaired activity of fibrinolytic system.

Acquired clotting factors deficiency may be resulted from antibodies formation against them; impaired synthesis of clotting factors in patients with vitamin K deficiency, liver failure, disseminated intravascular coagulation and after anticoagulants treatment. **Antibodies to clotting factors** may be referred to alloantibodies (after transfusion of concentrate of clotting factors in patients with coagulopathies) or autoantibodies (in patients with autoimmune diseases). In these cases screening for coagulation factors inhibitors is necessary. For instance, to suspect antibodies against FVIII, APT is measured in different dilutions of patient plasma in normal plasma. Absence of any changes in elevated APT after mixture patient plasma with normal donor plasma indicated possible presence of antibodies against FVIII.

Causes and outcomes of **vitamin K deficiency** were discussed in the Table 11-1 (“General pathophysiology: the essentials”).

Liver diseases complicated by portal hypertension may lead to life-threatening bleeding from varicose esophageal veins. Such bleeding has multiply mechanisms:

1. Thrombocytopenia resulted from sequestration of platelets in enlarged spleen.
2. Thrombocytopathia due to impaired platelet function following liver failure.
3. Coagulopathy caused by decreased synthesis of all clotting factors, except vWF and impairment of vitamin-K-dependent γ-carboxylation of II, VII, IX and X clotting factors as well as qualitative fibrinogen deficiency.
4. Increased activity of fibrinolytic system.

Disseminated intravascular coagulation (DIC) was defined by International Society of Hemostasis and Thrombosis in 2001 as “an acquired syndrome characterized by the intravascular activation of coagulation with loss of localiza-

tion arising from different causes. It can originate from and cause damage to the microvasculature, which, if sufficiently severe, can produce organ dysfunction." It has been estimated that DIC occurs in approximately 1 of every 1000 hospital patients.

Etiologic factors of DIC include severe infections, sepsis, obstetric complications (amniotic fluid embolism, abruptio placentae, septic abortion, retained dead fetus, preeclampsia), either shock, malignancies, severe trauma, fat embolism, burns, frostbite, exposure of snake venoms, intoxications, severe diseases such as acute pancreatitis, renal failure, liver failure, aortic aneurysms, giant hemangioma and transfusion reactions. According with clinical course, DIC can be acute, subacute and chronic. Pathogenesis of DIC is illustrated in the Fig. 1-29.

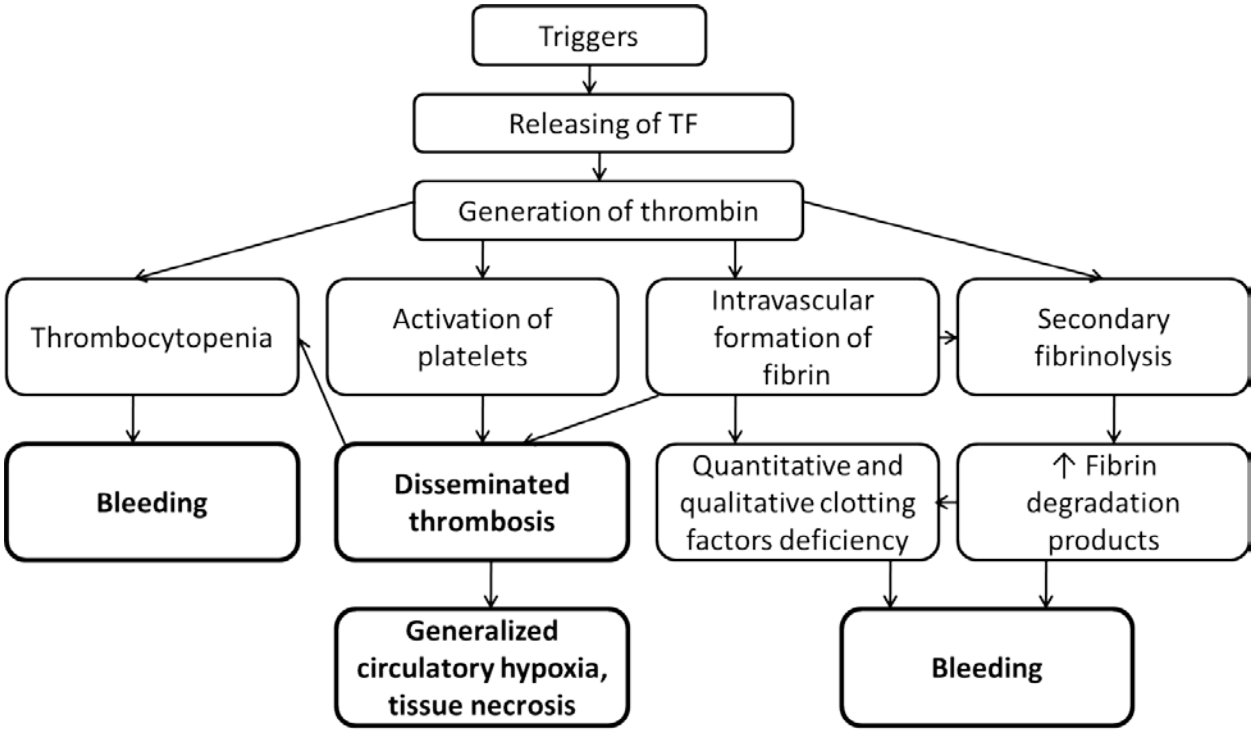


Figure 1-29. Simplified mechanisms of disseminated intravascular coagulation
TF, tissue factor

Severe injury leads to exposure of TF and initiates extrinsic pathway of blood coagulation. Proinflammatory cytokines, proteases, toxins, immune complexes, etc., may activate platelets and endothelial cells. Loss of athrombogenic surface of endothelial cells promotes platelets adhesion. Contact activation of blood coagulation (negatively charged surface of internal vascular wall, endotoxin, immune complexes, etc.) stimulates intrinsic pathway of coagulation. Prolonged inflammatory disorders are characterized by increased production of clotting factors by hepatocytes as a part of acute phase response (some clotting factors are acute phase proteins). These events are concerned to the 1st phase of DIC – activation of coagulation. The 2nd phase is characterized by a hypercoagulation stage and disseminated thrombosis with generalized circulatory hypoxia, specific signs of different organs damage and development of multiorgan failure. Cellular damage,

in turn, enhances inflammation thus making a "vicious circle". Due to microvascular thrombosis, microangiopathic hemolytic anemia begins to develop with fragmentation of RBCs (Fig. 1-30, Supplement). In order to front to excessive blood coagulation, anticoagulation system activates followed by it astonishing. Thrombin and fibrin also stimulate fibrinolytic system. The 3rd phase of DIC is in fact transition from hypercoagulation state to hypocoagulation. The situation is significantly impaired by thrombocytopenia and acquired coagulopathy because of platelets and clotting factors have been used for thrombi formation. Moreover, products of proteolytic fibrin cleavage (Fibrin Degradation Products, FDPs) disturb platelet function and clotting factors function. Hence, 4th phase of DIC – consumption coagulopathy and bleeding – reflects disorders in both primary and secondary hemostasis as an activation of fibrinolysis. The next 5th phase of DIC is outcome (recovery on the assumption of timely diagnosis and adequate treatment or death). High mortality rate in DIC (30-80%) is explained by close relations between DIC, systemic poorly controlled inflammation and multiply organ dysfunction syndrome.

Pathophysiologic basis for treatment of DIC: (1) correct treatment of underlying disorders which can lead to DIC and timely diagnosis of this complication by repeated (2-3 times per day) sampling of blood to detect platelet count, APT, PT (INR), fibrinogen, fibrin D-dimer and antithrombin; (2) unfractionated heparin in hypercoagulation state with a caution; (3) antithrombin concentrate but not in combination with heparin; (4) recombinant human activated protein C, which has been shown experimentally to inhibit coagulation and inflammation, but stimulate fibrinolysis; (5) fresh-stored or fresh-frozen plasma as a source of clotting factors, fibrinolytic factors and fibrinolysis inhibitors; (6) concentrate of depleted clotting factors in consumption coagulopathy and bleeding; (7) platelet infusion in case of documented thrombocytopenia; (8) inhibitors of fibrinolysis (tranexamic acid).

Bleeding disorders resulted from excessive fibrinolysis

To better understanding causes and mechanisms of bleeding disorders related to excessive fibrinolysis it is insistently recommended to read about this system in the textbook "General pathophysiology: the essentials", Part VIII and to study Fig. 8-2 in it. Disorders of fibrinolysis can be hereditary (rare) and acquired.

- α_2-antiplasmin deficiency as a hereditary disorder is very rare. Acquired α_2-antiplasmin deficiency is often seen in DIC, liver diseases and after thrombolytic treatment. Clinical signs in severe deficiency include muscle and joint bleeding resulted from decreased plasmin inhibition.
- Increased concentration of plasminogen activator released by prostate cancer cells and some leukemic cells. Plasminogen transforms to plasmin and dissolves fibrin clots. Besides affecting fibrin, the fibrinolytic activity of plasmin affects V, VIII, XIII clotting factors, large multimeric complexes vWF and reversibly impairs activity of platelet membrane receptors.
- Plasminogen activator inhibitor-1 deficiency was detected in several clinical studies in patients with postoperative bleeding. Increase in plasmin concen-

tration leads to bleeding.

- Decreased thrombin activatable fibrinolysis inhibitor is decreased in hemophilic patients, DIC and liver cirrhosis. This disorder enhances bleeding in such patients.
- Thrombolytic agents may cause excessive bleeding as an adverse side effect.
- Lack of activators of fibrinolysis clearance in liver failure.

Inhibition of fibrinolysis with tranexamic acid, which suppresses activation of plasminogen to plasmin, is indicated for treatment of bleeding associated with activation of fibrinolysis.

PART II. PATHOPHYSIOLOGY OF THE CARDIOVASCULAR SYSTEM

1. HEART FAILURE

Definition and classification of the heart failure

Heart failure (HF) is a clinical syndrome characterized by the inability of the heart to pump blood at an output sufficient to meet the requirements of metabolizing tissues or to do so only at abnormally elevated diastolic pressures or volumes. HF is classified to:

1. Acute and chronic heart failure. Acute HF develops suddenly and may lead to death. Chronic HF complicates different diseases of cardiovascular system, or metabolic disorders, or endocrine diseases; it progresses more slowly.
2. Left-sided HF, right-sided HF and total HF. It is necessary to point, that despite initial injury of selected heart chamber, with time all heart chambers will be involved in the pathological process with development of total HF.
3. Forward and backward HF. Symptoms of forward heart failure are result of the decreased ejection of the blood in the arterial vessels from the injured ventricle. Thus, symptoms of forward left ventricular failure include generalized tissue hypoperfusion with muscle weakness, fatigue, oliguria, etc. Symptoms of forward HF are resulted from lungs hypoperfusion and manifest as hypoxemia. Clinical signs of backward heart failure are caused by blood congestion in the vessels located higher than injured ventricle. Backward left ventricular failure causes blood congestion in the left atrium and pulmonary veins with development of cardiogenic pulmonary edema. Backward right ventricular failure results in blood congestion in the right atrium and vena cava superior and inferior with swelling of jugular veins, edema of extremities and liver enlargement.
4. HF with low and high cardiac output (CO). HF with low CO is seen in patients with ischemic heart disease, arterial hypertension, valvular heart disease, cardiac malformations and cardiomyopathies. HF with high CO may develop in patients with thyrotoxicosis, beri-beri, systemic arteriovenous shunting, and chronic anemia.
5. Systolic and diastolic HF. Systolic heart failure is a result of decreased myocardial contractility. Heart walls are thin. Systolic HF is confirmed by a reduced left ventricular ejection fraction (EF). EF = SV / EDLVP, where SV is a stroke volume, EDLVP is an end-diastolic left ventricular pressure. EF>50% is normal, whereas EF<50% is associated with reduced survival. That is why systolic HF is called as HF with reduced EF. Systolic HF often followed with sodium and water retention. This form of HF is often seen in males after myocardial infarction and patients with hereditary cardiomyopathies. Diastolic heart failure is caused mainly by altered ventricular relaxa-

tion or defects in diastolic filling. Heart walls are thick. Features of diastolic HF include rise of EDLVP, preserved ejection fraction (so-called HF with preserved EF) and signs of blood congestion in the systemic or pulmonary circulation. Aging individuals, patients with arterial hypertension and diabetes mellitus develop diastolic HF commonly. Pathogenesis of systolic and diastolic HF differs considerably.

6. According with New York Heart Association (NYHA), HF is subdivided into four functional classes: I – asymptomatic; II – symptoms of HF manifests with moderate exertion; III – patient becomes symptomatic with minimal exertion; IV – patient is symptomatic at rest.

Etiology of heart failure

Causes of HF are summarized in the Table 2-1.

Table 2-1. Causes of HF

Basic causes	Clinical examples
Volume overload	Regurgitant valves; Increased cardiac output: chronic anemia, thyrothoxicosis; beri-beri, arteriovenous fistula
Pressure overload	Outflow obstruction (aortic stenosis, pulmonary artery stenosis, mitral stenosis, etc.); Arterial hypertension
Loss of contractile elements	Myocardial infarction; Connective tissue diseases
Decreased myocardial contractility	Hereditary cardiomyopathies; Myocardial ischemia; Bacterial and viral infections; Poisoning (ethanol, cocaine, chemotherapeutic drugs, cobalt, etc.)
Decreased relaxation with decreased filling	Cardiac tamponade, pericardial effusion; Impaired relaxation in patients with amyloidosis
Disorders of cardiac rhythm (arrhythmias)	Tachyarrhythmia→shortening of diastole→decreased ventricular filling→decreased cardiac output+increased oxygen demand+impaired coronary blood flow; Bradyarrhythmia→decreased cardiac output

For future physicians it is important to know factors promoting decompensation of heart failure. These include discontinuation or non-adequate therapy, arrhythmias, myocardial ischemia or infarction, infections, pulmonary embolism, increased physical and/or emotional activity, myocarditis, concomitant diseases such as acute glomerulonephritis with renal failure, use of medications that can worse myocardial contractility (calcium antagonists, β-blockers) or promote fluid retention (estrogens, corticosteroids, nonsteroidal anti-

inflammatory drugs), cardiotoxins exposure and physiologic rise in cardiac output during pregnancy.

Pathogenesis of heart failure

Pathogenesis of acute heart failure was discussed in the Part XVI (Cardiogenic shock) in the textbook "General pathophysiology: the essentials".

During chronic heart failure changes affect several integrative levels. These abnormalities include

I. Changes in hemodynamic:
- Decreased stroke volume (in systolic dysfunction)
- Decreased ventricular filling (in diastolic dysfunction)
- Endothelial dysfunction

II. Neurohumoral changes:
- Sympatoadrenergic activation
- Activation of Renin-Angiotensin-Aldosterone System (RAAS)
- Vasopressine (ADH) secretion
- Decreased action of atrial natriuretic peptide (ANP)
- Increased production of endogenous digitalis-like factor
- Production of proinflammatory cytokines and systemic low grade inflammation

III. Cellular changes in cardiomyocytes and myocardium:
- Disorders of Ca^{2+} turnover
- Desensitization of adrenoreceptors
- Hypertrophy of cardiomyocytes
- Re-expression of "fetal" genes
- Epigenetic regulation of cardiomyocytes genes
- Excessive cellular death
- Myocardial fibrosis
- Cardiac remodeling

Changes in hemodynamic. To maintain decreased cardiac output during systolic dysfunction the heart can implement following compensatory mechanisms: (1) increased return of blood to the heart (increased preload) can stimulate contractility of sarcomeres via Frank-Starling mechanism with "expensive price" of such adaptation leading to increased end-diastolic pressure; (2) catecholamine-induced increase of cardiac output; (3) myocardial hypertrophy. Although each of these compensatory mechanisms can temporarily maintain cardiac output, each is limited in its ability to do so, and if the underlying reason for systolic dysfunction remains untreated, the heart ultimately fails. Diastolic dysfunction is characterized by impaired relaxation. However, systolic and diastolic dysfunction usually coexists. Endothelial dysfunction in patients with heart failure may facilitate vasoconstriction, thrombosis and rapid development of atherosclerosis.

Neurohumoral changes.

Increase of sympathetic activity occurs early in the development of heart failure. Mechanism of such activation can be explained as following: decreased stroke volume → "unloading" of high-pressure baroreceptors in the left ventricle, aorta and carotid artery → loss of inhibitory parasympathetic tone to the central nervous system → generalized increase in efferent sympathetic tone and release of antidiuretic hormone from the posterior pituitary. Short-term activation of sympathetic nervous system (SNS) may have beneficial effects during acute heart failure stimulating myocardial contractility. Nevertheless, SNS activation results in tachycardia, which increases myocardial oxygen demand. During chronic heart failure long-term activation of SNS will have detrimental outcomes including increase in systemic vascular resistance (SVR) and impaired end-organs perfusion; cardiotoxic and potentially proarrhythmogenic effects of catecholamines; catecholamine-induced necrosis of cardiomyocytes; myocardial hypertrophy, RAAS activation and desensitization of adrenoreceptors in the myocardium. The latter implies decrease in number of β_1-adrenoreceptors and/or alteration of G-proteins coupled signaling after catecholamines exposure. Desensitization of adrenoreceptors clinically develops by reduced cardiac output following physical and emotional activity. Above-mentioned explains pathophysiological basis for administration of β-adrenoblockers in optimal doses during chronic heart failure.

RAAS activation. RAAS functions both as a circulating (generalized) system and as a tissue paracrine/autocrine (local) system. The RAAS activation starts with the release of renin into the circulation from the juxtaglomerular cells of the kidney. Renin secretion is stimulated by (1) Na^+ depletion, (2) β-sympathetic stimulation, and (3) reduced renal perfusion. Active renin in the plasma cleaves angiotensinogen (produced by the liver) to angiotensin I, which is then converted by circulating and locally expressed angiotensin-converting enzyme (ACE) to angiotensin II (Fig. 2-1). ACE is a membrane-bound exopeptidase and is localized on the plasma membranes of various cell types, including vascular endothelial cells, microvillar brush border epithelial cells (e.g., renal proximal tubule cells), and neuroepithelial cells. ACE (also known as kininase II) metabolizes a number of other peptides, including the vasodilator peptides bradykinin and kallidin, to inactive metabolites.

Although Ang II is the primary active product of the RAAS, there is evidence that other metabolites of Ang I and II may have significant biological activity, particularly in tissues. Ang III and IV are formed by the sequential removal of amino acids from the N-terminus of Ang II by the action of aminopeptidases. Ang III [Ang-(2-8)], a heptapeptide formed by removal of the first N-terminal amino acid, is present in the central nervous system (CNS), where it is thought to play an important role in tonic blood pressure maintenance and in hypertension. Ang IV [Ang-(3-8)] is a hexapeptide formed by further enzymatic degradation of Ang III. In the brain, Ang IV increases blood pressure by cooperating with Ang II on angiotensin II type 1 (AT1)-receptor signaling.

Peptides truncated at the C-terminus of Ang II may also have biological activity. For example, Ang-(1-7), a heptapeptide fragment of Ang II, can be formed from Ang I or Ang II by the actions of several endopeptidases or from Ang II by the action of carboxypeptidases, including one with significant structural homology to ACE (which has been termed "ACE 2"). Unlike ACE, this enzyme does not convert Ang I to Ang II and its activity is not affected by ACE inhibitors (ACEIs). Ang-(1-7), which appears to act via a unique receptor, was first described to have vasodilatory effects and act as a natural ACEI. Cardioprotective effects have also been proposed to result from a direct effect of Ang-(1-7).

Angiotensin II interacts with different receptors. At least 4 angiotensin receptor subtypes have been described. Angiotensin II type 1 receptors (AT1R)-mediated effects involve actions on the cardiovascular system (vasoconstriction, increased blood pressure, increased cardiac contractility, vascular and cardiac hypertrophy), kidney (renal tubular sodium reabsorption, inhibition of renin release), sympathetic nervous system, and adrenal cortex (stimulation of aldosterone synthesis). The AT1 receptor also mediates effects of Ang II on cell growth and proliferation, inflammatory responses, and oxidative stress. The type 2 (AT2) receptor is abundant during fetal life in the brain, kidney, and other sites, and its levels decrease markedly in the postnatal period. AT2R-mediated actions are vasodilation, antiproliferative and apoptotic effects in vascular smooth muscle and inhibition of growth and remodeling in the heart. The type 4 (AT4) receptors are thought to mediate the release of plasminogen activator inhibitor 1 by Ang II and by the N-terminal truncated peptides (Ang III and Ang IV), but the function of the type 3 (AT3) receptors is unknown. The putative effects attributed to the C-terminal truncated peptide Ang 1-7, including vasodilatation, natriuresis, antiproliferation, and cardiac protection, are presumed to be mediated by a unique receptor that does not bind Ang II, most likely a product of the Mas proto-oncogene known as the Mas receptor.

Thus, overactivation of generalized RAAS during heart failure results in Ang II and aldosterone hyperproduction. Aldosterone, in turn, promotes Na^+ reabsorption and K^+ excretion. In that way activation of generalized RAAS leads to increased preload and afterload thus promoting progression of the heart failure.

Local or "tissue" Ang II biosynthesis may be initiated by renin and/or angiotensinogen taken up from the circulation. In addition, independent Ang II generating systems have been postulated to exist in the heart, peripheral blood vessels, kidney, brain, adrenal glands, pituitary, adipose tissue, testes, ovaries, and skin. Serine proteases, including several kallikrein-like enzymes (tonins), cathepsin G, and chymase are thought to contribute to Ang II formation in the tissue RAAS. Under physiological conditions, the apparent function of the cardiac RAAS is to maintain cellular balance of inhibiting and inducing cell growth, and proliferation and mediation of adaptive responses to myocardial stretch. Locally produced Ang II exerts an inotropic effect, mediates myocyte hypertrophy via the AT1 receptor, and is involved in cardiac remodeling. Pathologic activation of cardiac RAAS, perhaps through local upregulation of ACE levels, has been proposed to contribute

to the development and maintenance of left ventricular hypertrophy. Moreover, local RAAS activation induces myocardial fibrosis, arrhythmias, potentiates action of catecholamines on the heart and stimulates blood coagulation.

These data have established pathophysiological basis for the suppression of excessive RAAS activation during heart failure. List of applied groups of drugs include β-blockers, ACE inhibitors, AT1R-blockers and aldosterone antagonists.

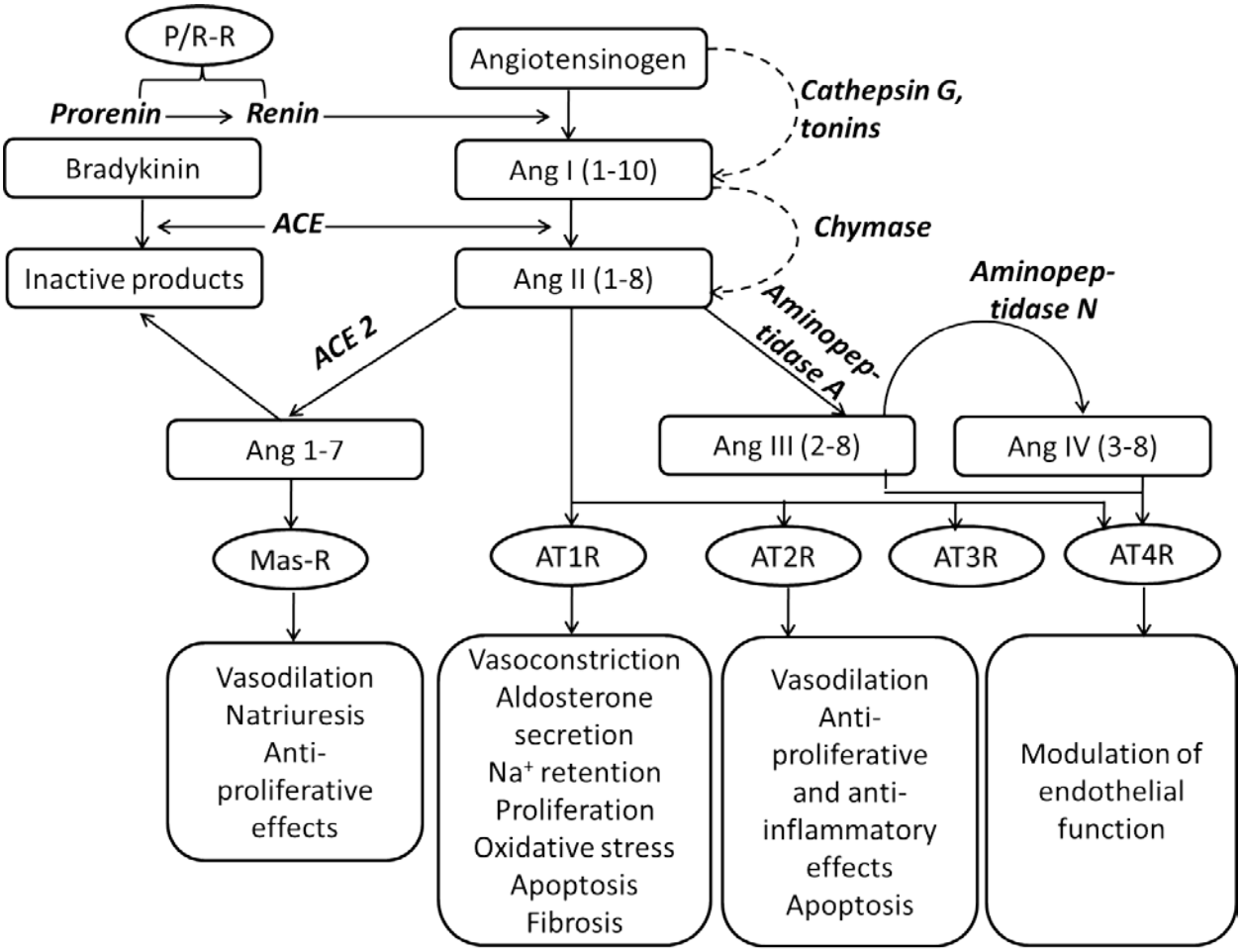


Figure 2-1. The RAAS

ACE, Angiotensin Converting enzyme; Ang I, Angiotensin I; Ang II, Angiotensin II; Ang III, Angiotensin III; Ang IV, Angiotensin IV; Ang 1-7, Angiotensin 1-7; ATR, Angiotensin Receptor subtype; Mas-R, Mas-receptor.
Dashed lines indicate alternative pathways for Ang I and Ang II formation

Heart failure associates with enhanced secretion of vasopressin (ADH). Loss of inhibitory parasympathetic nervous system tone on the CNS during HF triggers ADH secretion from the posterior pituitary. ADH is a potent vasoconstrictor and a stimulator of water reabsorption by renal collecting ducts. As a result, increase of preload and afterload are seen, which favors progression of heart failure.

Atrial natriuretic peptide (ANP) is a hormone of cardiac origin. It is released in response to atrial distension and participates in different regulatory mechanisms. Acting on kidneys, ANP increases glomerular filtration rate and induces diuresis thus decreasing preload. In the heart ANP delays cardiac remodeling and hypertro-

phy; in the vasculature it mediates vasodilation with subsequent decreased afterload. Moreover, ANP opposes to undesirable effects of SNS, RAAS, ADH and endothelin. Patients with HF have an increased concentration of ANP in the blood. Nevertheless, biological response to ANP in such patients is significantly attenuated due to: (1) releasing of less active forms of ANP during heart failure; (2) inadequate signaling after binding of ANP with receptors; (3) decreased renal perfusion pressure; (4) increased enzymatic degradation of ANP by neutral endopeptidases and/or elevated degradation rate of ANP's second messenger cGMP by specific phosphodiesterase; (5) strong activation of antagonizing systems including SNS, RAAS, ADH and a potent vasoconstrictor endothelin. Abovementioned facts give theoretical bases for action on ANP during HF by administration of human recombinant brain natriuretic peptide or inhibition of ANP degradation with neutral endopeptidases inhibitors.

Endogenous digitalis-like factor(s) are digitalis-like steroids which are synthetized, hypothetically, in adrenal glands and inhibit Na^+/K^+ ATPase in renal tubules and in vascular smooth muscle cells in "oubain-like" fashion. Level of endogenous digitalis-like factor in the blood during heart failure rises. This leads to impairment of natriuresis, vasoconstriction and cardiac remodeling. Several functional antagonists of endogenous digitalis-like factor have been tested to reverse it effects – anti-digoxin and anti-oubain antiserum and steroid receptor antagonists of this factor.

HF associates with increased level of proinflammatory cytokines and systemic low grade inflammation. Generalized tissue hypoperfusion resulted from decreased CO and peripheral vasoconstriction leads to circulatory hypoxia, cellular damage and development of "sterile" inflammation after activation of immune cells by Damage-Associated Molecular Patterns (DAMPs). In response immune cells begin to synthetize proinflammatory cytokines IL-1, IL-6 and TNF-α. Another stimulus initiating inflammation is a hypoperfusion of the gut. Associated bacterial enteral translocation results in endotoxinemia. Endotoxin is a potent activator of different cells, including leukocytes and endothelial cells. High level of proinflammatory cytokines in patients with heart failure was detected. Proinflammatory cytokines suppress myocardial contractility, participate in cardiac remodeling, lead to oxidative and nitrozative stress, stimulate rate of cardiomyocytes loss in the failing heart, and impair ATP synthesis in the heart. Proinflammatory cytokines also lead to endothelial dysfunction, cachexia in advanced stages of heart failure and acute phase response.

Cardiac remodeling

Cardiac remodeling is a dynamic process in which the heart undergoes structural changes in response to hemodynamic overload or myocardial injury with subsequent misbalance between cellular and acellular components in the heart including: changes in chambers' size and shape; changes of myocardial mass; changes of interstitial structures. These changes affect several integrative levels – cellular (cardiomyocytes), tissue (myocardium) and organ (whole heart). Changes on the

cellular level include abnormal excitation-contraction coupling, fetal genes expression, desensitization of adrenoreceptors and hypertrophy.

Abnormal excitation-contraction coupling. The initiating event in excitation-contraction coupling is firing of the action potential, which leads to Ca^{2+} influx via the L-type Ca^{2+} current (LTCC, Fig. 2-2). This Ca^{2+} influx activates the Ca^{2+} release channels found on the sarcoplasmic reticulum – the ryanodine receptors (RyR) – causing a graded release of Ca^{2+} from the sarcoplasmic reticulum, a process termed Ca^{2+}-induced Ca^{2+} release. The myofilaments are, in turn, activated by this increase in Ca^{2+}concentration such that there is a direct, though nonlinear, relationship between free Ca^{2+} concentration and contraction. After activation, the Ca^{2+} concentration returns to diastolic levels via uptake by the sarcoplasmic/endoplasmic reticulum calcium ATPase/phospholamban (SERCA/PLB) complex and the Na^{+}/Ca^{2+} exchanger (NCX), a process that also contributes to the action potential waveform.

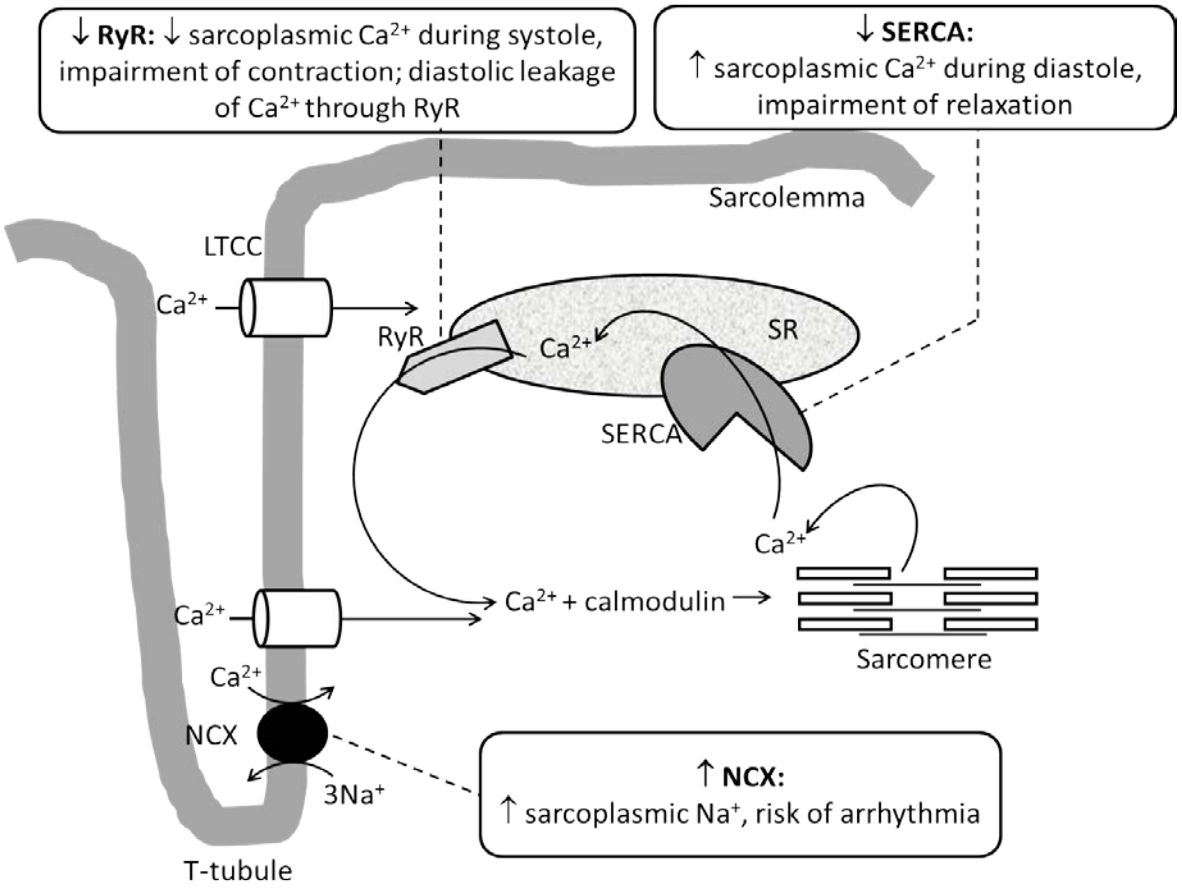


Figure 2-2. Simplified presentation of Ca^{2+} cycling in the cardiomyocytes

LTCC, L-type Ca^{2+} channel; NCX, Na^{+}/Ca^{2+} exchanger; RyR, ryanodine receptor; SERCA, Ca^{2+}-ATPase; SR, sarcoplasmic reticulum

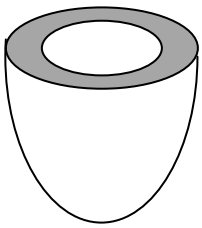
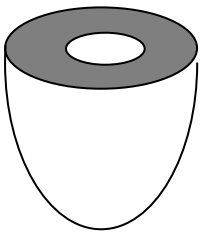
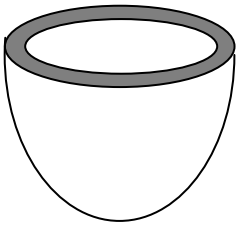
In blocks connected with dashed lines changes of Ca^{2+} cycling in the failing heart and their clinical significance are summarized.

The cardiac dysfunction in HF can be observed at the cellular level as a blunted force-frequency response. Much of this dysfunction is due to changes in the expression of certain proteins such as transient outward potassium channels, inward rectifier potassium channels, NCX, ryanodine receptors and SERCA, among others. These protein expression changes lead to increased action potential duration, reduced Ca^{2+} transient and shortening amplitude, and slowed rates of cytosolic Ca^{2+} decline and relaxation.

Fetal genes re-expression in the failing heart. HF associates with changes in cardiomyocytes phenotype and synthesis of fetal isoforms of contractility proteins. For instance, decrease production of myosin heavy chain-α (with high ATPase activity or "fast myosin") occurs. Ratio between α- and β- ("slow") myosin in the cardiomyocytes shifts. These alterations, together with impairment production of proteins regulating contraction of cardiomyocytes (myosin light chain, troponin T, troponin I) result in disturbances of myocardial contractility and impaired cardiomyocytes relaxation with development of diastolic dysfunction.

Hypertrophy. Cardiomyocytes cannot proliferate; thus hemodynamic overload and injury trigger program of cardiomyocytes enlargement, or hypertrophy. Hypertrophy may be physiological (following normal pregnancy, aerobic exercises) or pathological. Different types of loads result in concentric or eccentric hypertrophy (Table 2-2).

Table 2-2. Concentric vs. eccentric myocardial hypertrophy

Criteria	Concentric hypertrophy	Eccentric hypertrophy
Type of overload	Pressure overload	Volume overload
Increased pressure	Systolic	Diastolic
Type of new myofibrils addition	Parallel	Series
Thickness of cardiac wall	↑	Normal, ↑ or ↓ depending on stage of disease
Size of chamber	Normal or ↓ depending on stage of disease	Normal or ↑ depending on stage of disease
Schematic illustration  Normal ventricle		

Mechanism of hypertrophy can be simplified as following events sequence: ↑ mechanical load on cardiomyocytes, action of growth factors, ROS and RNS, proinflammatory cytokines, catecholamines, Ang II, aldosterone, endothelin-1, etc. on cardiomyocytes → recognition of mechanical and biochemical stimulus (by superficial integrins, ion channels, receptors to growth factors, proteins in gap junctions, α1-adrenoreceptors, AT1R, mineralocorticoid receptors, receptors to endothelin-1, etc.) → activation of multiply intercellular signaling pathways → activation of genes c-fos, c-jun, c-myc; reactivation of fetal genes → ↑ synthesis of proteins → hypertrophy of cardiomyocytes, myocardial hypertrophy.

Biological significance of hypertrophy is controversial. On the one hand, according with Laplace's law,

$$\text{Wall tension} = \frac{\text{Intraventricular pressure} \times \text{Radius of ventricle}}{2 \times \text{Thickness of ventricular wall.}}$$

This means, that hypertrophy will decrease mechanical load on the separate cardiomyocyte and improve myocardial contractility during certain time. On the other hand, hypertrophy will result in the gradual progression of heart failure via following mechanisms: (1) hypertrophied cardiomyocytes requires additional amounts of oxygen; (2) angiogenesis and growth of nerves lag behind myocardial hypertrophy thus making predisposition for ischemic episodes and arrhythmia; (3) ATP deficiency in the hypertrophied cardiomyocytes; (4) diastolic dysfunction; (5) accelerated death of cardiomyocytes. That is why cardiac hypertrophy is an independent risk factor of sudden cardiac death.

Pathological cardiac remodeling in the onset of hypertrophy and heart failure can be viewed, at least in part, as a transcriptional disorder and that normalization of the gene expression pattern of the cardiac myocyte through transcriptional therapies (selective protein kinases inhibitors, histone deacetylases inhibitors, etc.) represents a promising approach for cardiac therapy.

Remodeling affects heart on the tissue level. These changes include excessive loss of cardiomyocytes and multidirectional alterations in extracellular matrix (fibrosis or degradation of extracellular matrix).

Excessive loss of cardiomyocytes. Approximately 38 million of cardiomyocytes die every year in healthy old persons. Despite this, myocardial mass is preserved on the relatively constant level owing to myocardial hypertrophy. Rate of cardiomyocytes death significantly increases in patients with HF. Three types of cardiomyocytes death: necrosis, apoptosis and autophagy are responsible for progressive decline in cardiomyocytes number during HF and decrease of myocardial contractility. Main stimulus for accelerated premature death of cardiomyocytes in the failing heart are: increased sympathetic drive (through β-AR), increased ROS and RNS formation, elevated Ang II production, raised myocardial mechanical strain and oxygen deficiency. The latter also leads to ATP deficiency, which is intensified by reduction of creatine kinase activity and decrease ratio between creatine phosphate and ATP.

Changes in extracellular matrix. Quantity and quality of extracellular matrix in the heart depend on the balance between formation of collagen fibers, prote-

oglycans, fibronectin and their degradation. Rate of extracellular matrix degradation, in turn, depends on the balance between matrix metalloproteinases and their inhibitors. Necrotic death of cardiomyocytes triggers "sterile" inflammation with synthesis of different growth factors including transforming growth factor-β (TGF-β). These growth factors stimulate fibroblasts to produce components of extracellular matrix. Excessive fibrosis associates with increase of myocardial stiffness and poor diastolic relaxation. Myocardial fibrosis may also worse microcirculation and impairs propagation of electric impulses in the failing heart. Activation of metalloproteinases with excessive degradation of collagen fibers will lead to disorders of interactions between adjacent cardiomyocytes and dilation of heart chambers.

Cardiac remodeling also affects **geometry of heart chambers**. In respect to the left ventricle, these changes include dilation, increased sphericity, wall thinning (Fig. 2-3) and mitral valve incompetence as a result of dysfunction of papillary muscles with subsequent volume overload of the left part of the heart and decline of myocardial contractility.

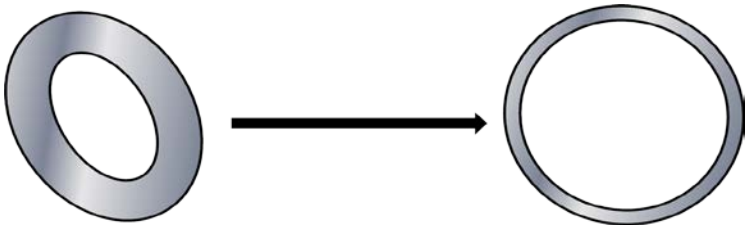


Figure 2-3. Schematic representation of geometric changes of the left ventricle in advanced stage of cardiac remodeling

In the normal left ventricle, stroke volume increases over a wide range of end-diastolic volumes (the Frank-Starling effect). If contractility is enhanced, such as during exercise or catecholamine stimulation, this increase is correspondingly greater. In the failing heart with spherical left ventricle and depressed myocardial contractility, there is relatively little increment in systolic function with further increases in LV volume. Thus Frank-Starling effect will be impaired. Spherical form of the left ventricle also associates with increased risk of arrhythmia and subendocardial ischemia, states which both will impair myocardial contractility.

Pathogenesis of symptoms of heart failure

Acute heart failure manifests as cardiogenic shock or acute cardiogenic pulmonary edema. Chronic heart failure develops more slowly. Left-sided heart failure often manifests by changes in the respiratory system. These changes and their mechanisms are illustrated in the Fig. 2-4. Clinically symptoms are displayed by dyspnea, ortopnea and pulmonary edema. Dyspnea is perceived shortness of breath. Shortness of breath occurs in the recumbent position (orthopnea) because of reduced blood pooling in the extremities and abdomen and because any increase in blood return leads to marked elevations in ventricular pressures. Patients usually learn to minimize orthopnea by sleeping with the upper body propped up by two or

more pillows. Sudden onset of severe respiratory distress at night – paroxysmal nocturnal dyspnea develops because of the reduced adrenergic support of ventricular function that occurs with sleep, the increase in blood return and normal nocturnal depression of the respiratory center.

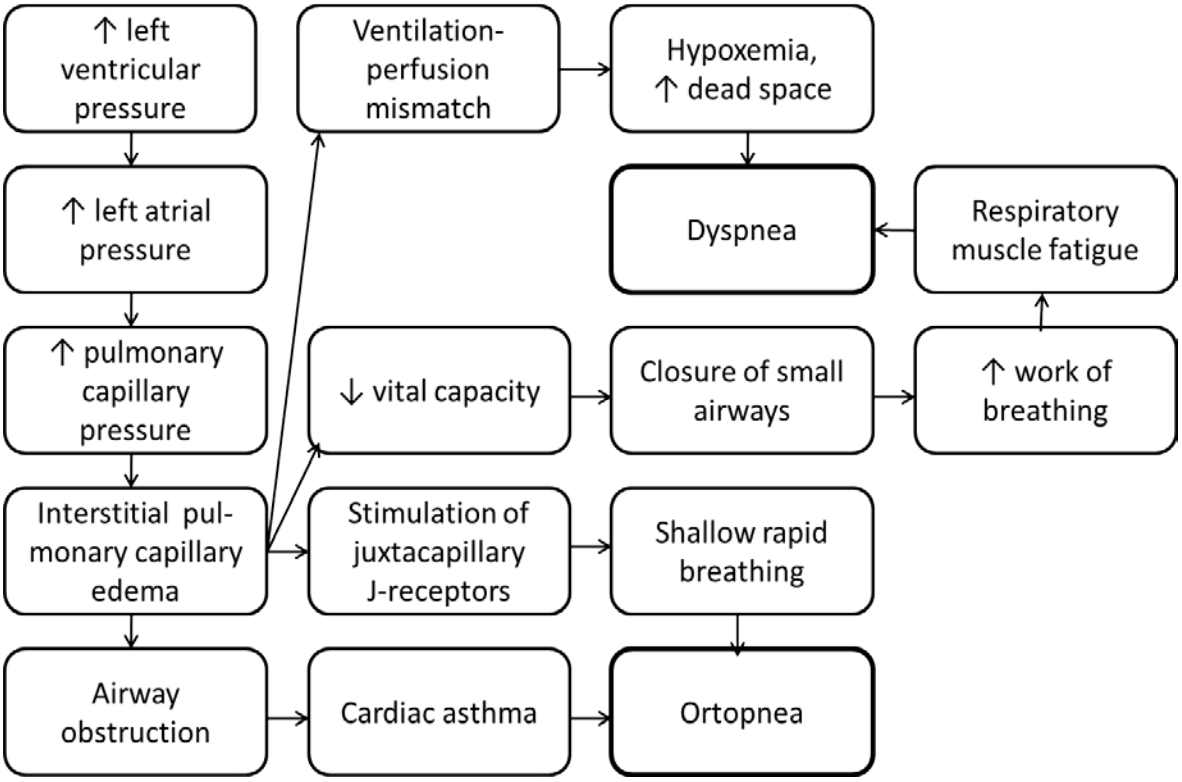


Figure 2-4. Pathogenesis of symptoms related to the respiratory system during left-sided heart failure

Pathogenesis of fatigue can be presented as following sequence: ↓ cardiac contractility → ↓ supply of skeletal muscles with blood → hypoxia → injury, low-grade inflammation, action of proinflammatory cytokines → dystrophy, fatigue. Confusion is resulted from hypoperfusion of the brain. Patients with heart failure often have cold pale skin due to systemic vasoconstriction as a result of excessive activation of SNS and RAAS.

Backward failure of right heart results in the increase in pressure in the systemic venous system with subsequent development of peripheral edema, hepatomegaly and ascites. Pathogenesis of edema during heart failure was discussed in details in the Textbook “General pathophysiology: the essentials” (See Fig. 12-2). Nocturia, or a predomination of urination during night time, is explained by a normalization of decreased renal perfusion during day time in supine position during night.

Patients with heart failure are in the group of increased risk of arrhythmia and sudden death owing to mechanisms summarized in the Fig. 2-5.

Cardiac cachexia is seen in patients with advanced stage of chronic heart failure and has a poor prognosis. It is resulted from systemic low-grade inflamma-

tion and action of proinflammatory cytokines. Increased catabolic rate, poor appetite and malabsorption are basic mechanisms of cardiac cachexia.

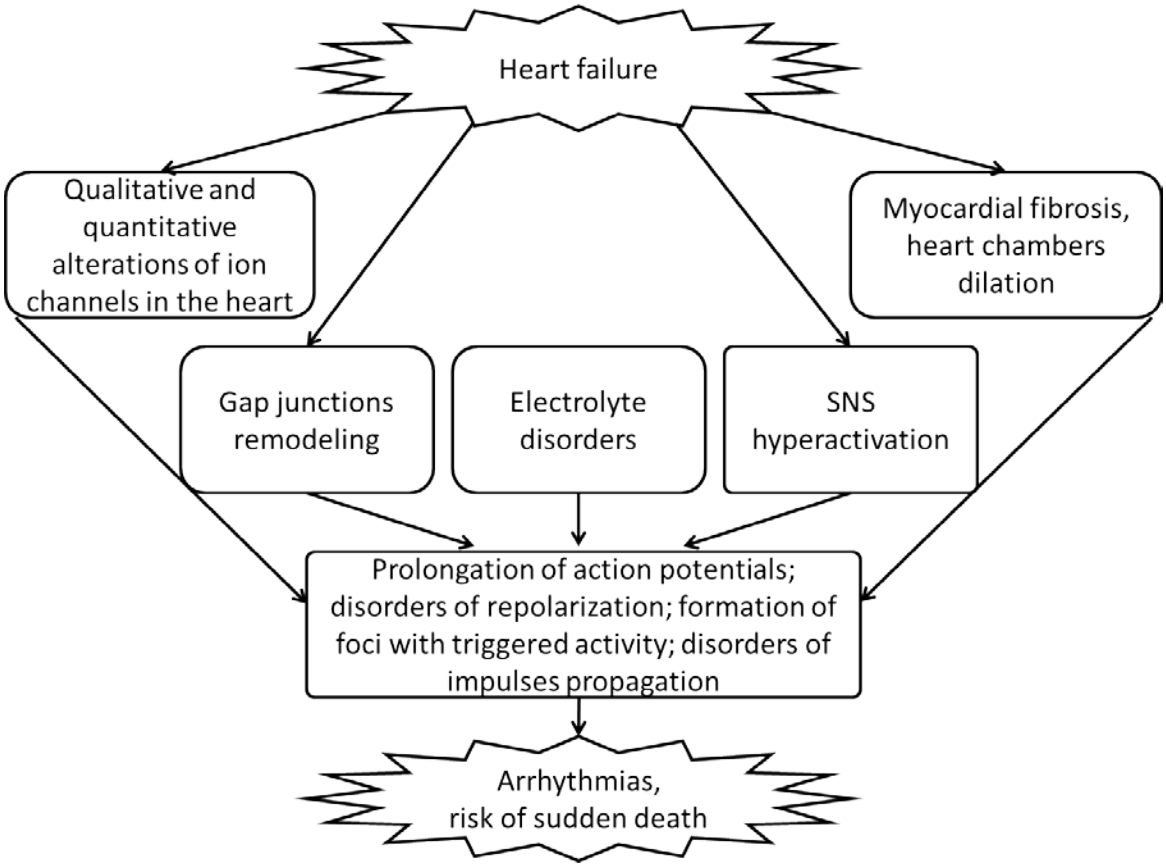


Figure 2-5. Pathogenesis of arrhythmia in patients with heart failure

Pathophysiologic basis for treatment of HF. Management of chronic heart failure requires adequate treatment of underlying disease. Treatment approaches include groups of drugs:

- Affecting RAAS activity – ACE inhibitors, Ang II receptor blockers and aldosterone antagonists (See Fig. 2-1). These groups of drugs are able to decrease activity both generalized and local RAAS and delay cardiac remodeling.
- β-adrenoblockers suppress SNS activity, decrease heart rate and decrease myocardial oxygen requirements.
- Peripheral vasodilators (hydralazine, nitrates). Hydralazine is an arterial vasodilator simultaneously preventing production of superoxide radical $O_2^{\cdot}$. This radical can inactivate a potent vasodilator nitric oxide NO. Thus, hydralazine prevents oxidative stress and prolongs half-life of NO. Nitrates are exogenous donors of nitric oxide thus dilating both arteries and veins and decreasing preload and afterload in patients with heart failure.
- Cardiac glycosides are used in patients with advanced stages of HF. Digitalis glycoside inhibit membrane Na^+/K^+-ATPase in cardiomyocytes with corresponding rise of $[Ca_2^+]_i$ in these cells and increasing of myocardial

contractility. However, cardiac glycosides have a lot of adverse effects and unable to delay cardiac remodeling effectively.

- Prophylaxis of thromboembolic complications (See Part VIII in the Textbook "General pathophysiology: the essentials").
- Invasive and surgery interventions: implantation of cardioverter-defibrillator for prophylaxis and correction of life-threatening arrhythmia, cardiac resynchronization therapy, revascularization therapy in patients with ischemic heart disease, left ventricle assist device and cardiac transplantation.

During acute HF main goals of treatment are: (1) reduction of both preload and afterload with diuretics, arterial and venous vasodilators (hydralazine, nitrates, morphine); (2) positive inotropic support (dopamine, dobutamine) and (3) positive airway pressure.

Selected valvular heart diseases

All valvular heart diseases can be classified into congenital and acquired; hemodinamically with a predomination of narrowing (stenosis) and with a leak (regurgitation).

Etiology of acquired valvular heart disease with a predominance of a stenosis:

- Rheumatic diseases;
- Degenerative diseases (in aging persons with advanced atherosclerosis, especially in patients with diabetes mellitus and atherosclerosis and/or hypercholesterolemia);
- Myxoma (atrial benign neoplasm), which may lead to mitral stenosis;
- Excessive Ca^{2+} deposition in the soft tissues.

Valvular heart disease with regurgitation may be resulted from cusp abnormalities, vessel dilation or ruptured chordae. Acquired valvular heart disease with cusp abnormalities may be caused by:

- Endocarditis;
- Rheumatic diseases;
- Ankylosing spondylitis.

Vessel dilation may be due to:

- Aneurysm;
- Heritable diseases of connective tissue;
- Inflammation (Takayasu disease, syphilis, arthritic diseases, cystic medial necrosis).

Ruptured chordae are resulted from trauma or dissection.

Let's discuss cardiac and systemic hemodynamic in patients with common valvular heart disease.

Aortic stenosis. The normal area of aortic valve is approximately 3.5-4.0 cm^2. Critical stenosis develops after decrease of the square less than 0.8 cm^2. The sequence of events in aortic stenosis is following: aortic stenosis → outflow obstruction → left ventricular pressure overload → concentric hypertrophy of the left

ventricle → cardiac remodeling → decompensation with pulmonary congestion. Often patients with aortic stenosis demonstrate symptoms of angina pectoris due to insufficient blood flow in the hypertrophied myocardium, concomitant coronary artery disease and coronary arteries embolization with calcium-containing emboli in patients with calcified aortic valve. Syncope may develop in patients with aortic stenosis resulted from fixed obstruction and brain hypoperfusion.

Aortic regurgitation can be acute or chronic. Pathogenesis of chronic aortic regurgitation: volume overload of the left ventricle → increased diastolic pressure → fiber elongation due to serial addition of sarcomeres → eccentric hypertrophy of the left ventricle → rise in stroke volume according with Starling's mechanism → cardiac remodeling → failure of Starling's mechanism → decreased myocardial contractility. Pulmonary edema may develop in affected patients. Acute aortic regurgitation doesn't lead to any compensatory mechanisms; aortic collapse, dyspnea and pulmonary edema develop suddenly.

Mitral stenosis is resulted from decrease normal mitral valve area (5-6 cm^2). Clinical symptoms develop after decreasing the area less than 1 cm^2. Pathogenesis of hemodynamic changes in patients with mitral stenosis: left atrium pressure overload → concentric hypertrophy of the left atrium → left atrial pressure elevation → elevated pulmonary venous pressure → right ventricle overload → reduced systolic function of the right ventricle → hypoxemia. Clinical symptoms include dyspnea, ortopnea, atrial arrhythmias resulted from increased left atrial size and increased risk of thromboembolic complications.

Mitral regurgitation may develop acute or chronically. Pathogenesis of hemodynamic changes in gradually developing is following: regurgitation of blood from the left ventricle into the left atrium → volume overload of the left atrium → eccentric hypertrophy of the left atrial → decompensation with time → clinical symptoms. These include pulmonary edema, fatigue and arrhythmias. Suddenly developed mitral regurgitation fails compensatory mechanisms with ortopnea, pulmonary edema and shock.

Pulmonic stenosis is a congenital disease due to fusion of pulmonic valve cusps. This disorder results in the pressure overload of the right ventricle and its concentric hypertrophy. Decreased contractility of the right ventricle results in hypoxemia, whereas dilation of the left ventricle in advance stage of disease leads to dilation of the right atrium, jugular veins distension, hepatomegaly and ascites.

Tricuspid stenosis results in the right atrium pressure overload, its concentric hypertrophy and clinical signs of the right-sided heart failure.

Tricuspid regurgitation leads to volume overload of the right ventricle, its eccentric hypertrophy and signs of right-sided HF including edema, ascites and liver enlargement.

Cor pulmonale

Cor pulmonale is a change in the structure and function of the right ventricle caused by a primary disorder of the respiratory system. Primary abnormalities of the left side of the heart or congenital heart disease are not considered cor pul-

monale. Pulmonary hypertension is the common link between lung dysfunction and the heart in cor pulmonale. Cor pulmonale may be acute or chronic (most commonly).

Acute cor pulmonale may be due to pulmonary embolism or acute respiratory distress syndrome (ARDS). The underlying pathophysiology in massive pulmonary embolism causing cor pulmonale is the sudden increase in pulmonary resistance. In ARDS, 2 factors cause right ventricular overload: the pathologic features of the syndrome itself and mechanical ventilation. Mechanical ventilation, especially higher tidal volume, requires a higher transpulmonary pressure.

Chronic cor pulmonale is resulted from following basic pathogenetic mechanisms:

- Pulmonary vasoconstriction due to alveolar hypoxia or blood acidemia (hypoxic pulmonary vasoconstriction).
- Anatomic compromise of the pulmonary vascular bed secondary to parenchymal or alveolar lung disorders (eg, emphysema, pulmonary thromboembolism, interstitial lung disease, ARDS, and rheumatoid disorders) leading to the elevated pulmonary blood pressure. Chronic obstructive pulmonary disorder is the most common cause of cor pulmonale.
- Increased blood viscosity secondary to blood disorders (eg, polycythemia vera, sickle cell disease, macroglobulinemia)
- Increased blood flow in pulmonary vasculature.
- Idiopathic primary pulmonary hypertension.

The result of the above mechanisms is increased pulmonary arterial pressure.

The right ventricle is a thin-walled chamber, which adapts better to changing preloads than afterloads. With an increase in afterload, the right ventricle increases systolic pressure to keep the gradient. At a point, a further increase in the degree of pulmonary arterial pressure produces significant right ventricle dilatation, an increase in right ventricle end-diastolic pressure, and right ventricle circulatory collapse. A decrease in right ventricle output with a decrease in diastolic left ventricle volume results in decreased left ventricle output. Because the right coronary artery, which supplies the RV free wall, originates from the aorta, decreased left ventricle output diminishes blood pressure in the aorta and decreases right coronary blood flow. What ensues is a vicious cycle between decreases in left ventricle and right ventricle output.

The clinical manifestations of cor pulmonale are generally nonspecific. The patient may complain of fatigue, tachypnea, exertional dyspnea, and cough. Anginal chest pain can also occur and may be due to right ventricular ischemia (it usually does not respond to nitrates) or pulmonary artery stretching. A variety of neurologic symptoms may be seen due to decreased cardiac output and hypoxemia. Hemoptysis (presence of the blood in the sputum) may occur because of rupture of a dilated or atherosclerotic pulmonary artery. In advanced stages, passive hepatic congestion secondary to severe right ventricular failure may lead to anorexia, right upper quadrant abdominal discomfort, and jaundice. In addition, syncope with exertion, which may also be seen in severe disease, reflects a relative inability to in-

crease cardiac output during exercise with a subsequent drop in the systemic arterial pressure. Elevated pulmonary artery pressure can lead to elevated right atrial, peripheral venous and capillary pressure. By increasing the hydrostatic gradient, it leads to transudation of fluid and accumulation of peripheral edema. A decrease in glomerular filtration rate and filtration of sodium and stimulation of arginine vasopressin play important pathophysiologic roles in the development of edema.

2. ATHEROSCLEROSIS. ISCHEMIC HEART DISEASE

Atherosclerosis

Atherosclerosis is one of the major underlying causes of cardiovascular diseases, related with high morbidity and mortality. Atherosclerosis is a multifactorial inflammatory disease affecting predominantly intimal and medial layers of large and middle-sized muscular and elastic arteries. The term "atherosclerosis" consists from two parts reflecting the nature of lesions: "ather" – "porridge" indicates soft lipid-rich lesion and "sclerosis" describes presence of fibrous component. The hallmark of atherosclerosis is an accumulation of lipids in intima with subsequent recruitment of inflammatory cells and gradually developed narrowing of artery's lumen. Erosion of atherosclerotic plaques leads to the thrombus formation and sudden ischemia with dramatic clinical manifestations depending on the site of atheroma location (Table 2-3).

Table 2-3. Clinical consequences of atherosclerosis

Localization of atherosclerotic lesions	Clinical complications
Plaques in coronary arteries	Ischemic heart disease (sudden coronary death, angina pectoris, myocardial infarction, heart failure, cardiac arrhythmias)
Plaques in cerebral arteries	Brain ischemia (transient cerebral ischemic attacks, stroke, encephalopathy, dementia)
Plaques in mesenteric arteries	Abdominal claudication, bowel infarction, malabsorption syndrome
Plaques in peripheral arteries	Intermittent claudication, gangrene
Plaques in renal arteries	Renal artery stenosis, renal failure, secondary renovascular arterial hypertension, infarction of kidneys
Aneurysms (in the aorta, iliac and popliteal arteries, in cerebral arteries)	An aneurysm is a localized vascular dilation resulted from congenital and/or acquired stretching of the vascular wall. Occlusive or hemorrhagic symptoms depending on the severity and location of aneurysm are common.

Risk factors for atherosclerosis can be classified into:

I. Correctable and non-correctable (sex, age and genetic predisposition).
II. Main (arterial hypertension, atherogenic dyslipidemia, smoking and diabetes mellitus) and secondary (sedentary life-style, obesity, stressful environment, incorrect diets, excessive alcohol consumption, systemic low grade inflammation, hyperhomocysteinemia, sleep disturbances, etc.).

Atherosclerosis is a slowly developed disease. Natural history of coronary atherosclerosis progression is represented in the Fig. 2-6.

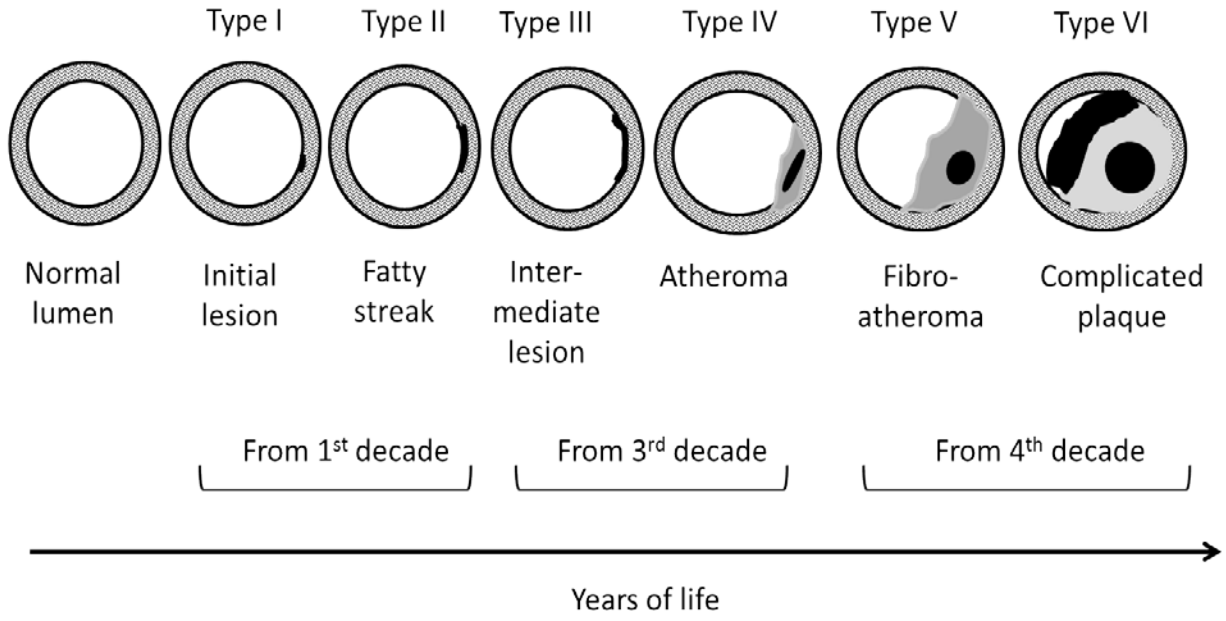


Figure 2-6. Progression of coronary atherosclerosis
See explanations in the text.

Development of atherosclerotic plaque progresses through six stages. Initial atherosclerotic lesion (Type I) which is characterized by a presence of foam cells can be detected even in fetus intrauterine with postnatal regression or, in contrast, progression. Foam cells are macrophages accumulating lipids intracellular. Artery lumen is normal. Type II (fatty streak) is characterized by an expansion of intracellular lipids accumulation in foam cells migrating in the intima. Intermediate lesion (Type III) is a result of the accumulation of lipids not only intracellular, but also extracellular. Next IV type, atheroma, has a discernible core from extracellular lipids, "cap" and "shoulders". Angiography (injecting a contrast agent into the arteries and imaging the lumen of the arteries with X-rays) may reveal stenoses or aneurysms consistent with atherosclerosis. Coronary artery angiography is the primary manner in which coronary artery atherosclerosis is currently diagnosed. A major limitation of traditional angiography is that it primarily images the lumen of the artery and not the vessel wall. During the asymptomatic part of the atherosclerosis history, an atheroma grows up outward, preserving the caliber of lumen resulting in understimation of the degree of atherosclerosis during arterial coronarography (so-called "phenomenon of compensatory enlargement"). Type V of atherosclerotic lesion is a fibroatheroma, which is characterized by enlargement core, strengthening of fibrous cap due to proliferation of vascular smooth muscle cells, activation of fibroblasts, synthesis of collagen fibers and calcification. Critical stenosis of the arterial lumen with appearance of clinical signs of ischemia occurs usually at approximately 70% fixed occlusion. Type VI (complicated lesion) results in acute clinical symptoms which are caused by (1) ulceration of fibrous cap with subsequent thrombosis and (2) bleeding in the plaque.

Pathogenesis of atherosclerosis can de described by several steps:

- Different risk factors for atherosclerosis results in the endothelial dysfunction (See Part VI in "General Pathophysiology: the essentials") with further increasing of vascular permeability.
- Excess low density lipoproteins (LDL) infiltrate the artery and are retained in the intima, especially at sites of hemodynamic strain (arterial bifurcations, aneurysms, etc.).
- Macrophages migrating in the intima and subintimal space active participate in the oxidative and enzymatic modifications of LDL.
- Chemically modified LDL, in turn, support endothelial dysfunction with stimulating of expression by activated endothelial cells adhesion molecules ICAM-1 and VCAM-1 with subsequent adhesion of monocytes to the activated endothelial cells.
- Macrophages in the vascular wall phagocytose modified LDL with foam cells formation. Vascular smooth muscle cells (vSMCs) also have ability to phagocytose modified LDL and to transform in the foam cells.
- Recruitment of new monocytes to the activated endothelial cells is seen. Monocytes then differentiate to the macrophages into the vessel wall.
- Interaction of microbial and self "danger signals for the immune system" with according pathogen related receptors enhances "infectious" and/or "sterile" inflammation (See Fig. 9-1 in "General pathophysiology: the essentials") with subsequent macrophage activation.
- Activated macrophages, endothelial cells, vascular smooth muscle cells produce proinflammatory cytokines, chemokines, ROS, RNS, proteases and other mediators participating in the inflammatory process in the arterial wall. These mediators together with activated leukocytes cause secondary damage of the vascular wall. Proinflammatory cytokines (IFN-γ, IL-1, TNF) stimulate IL-6 production with subsequent development of systemic low grade inflammation. Acute phase reactants (CRP, serum amyloid A, fibrinogen), together with other markers may help to prove diagnosis of atherosclerosis. Polarization of immune response with presumably Th1 differentiation is observed. T-regulatory cells through IL-10 and TGF-β can modulate inflammatory response.
- Activated macrophages produce growth factors (PDGF, FGF, TGF-α), which stimulate vSMCs and fibroblasts proliferation. "Secreting phenotype" of vSMCs is defined as their ability to fail to contract but synthesize extracellular matrix components (mainly collagen and elastin fibers). Such plaque fibrous cap is formed. Different factors influence on the plaque stability. Plaques' vulnerability is a function of increased numbers of macrophages, increased expression of tissue factor, reduced numbers of smooth muscle cells, a lipid core that occupies a high proportion of plaque volume, and a thin cap. When all of these factors coincide, the plaque is at high risk of disruption. Balance between proteases and their inhibitors significantly influence on the atherosclerotic plaque stability.

- Ulceration of fibrous cap triggers thrombosis (damaged fibrous cap is, in fact, 1st component of Virchow's triad), almost compete obstruction of arterial lumen and ischemia. Ischemia is supported by exaggerated vasoconstrictor response of artery with atheroma caused by (1) increased sensitivity of vSMCs to adrenergic signalling, (2) locally released vasoconstrictors from activated platelets, (3) endothelial dysfunction one of the hallmark of which is imbalance between vasodilators (mainly nitric oxide) and vasoconstrictors (endothelin), (4) probable dysfunction of perivascular cells and adipose-tissue surrounding cells.

Atherogenesis depends on both genetic and environmental factors. Hereditary causes (atherogenic hyperlipoproteinemias Type IIa, IIb, III, see Table 11-6, in "General pathophysiology: the essentials") associates with accelerated, premature atherosclerosis. Complete loss of LDL receptor (LDLR) due to loss of gene encoding of LDLR or functional abnormalities of the protein results in several fold increase in plasma cholesterol levels compared with the general population and also premature atherosclerosis. Rare genetic variation of the ApoE alleles results in dyslipoproteinemia and accelerated atherosclerosis. Normally, ApoE is necessary for the uptake of chylomicron and VLDL remnants from the blood via the LDLR and the LDL receptor-related protein. Apolipoprotein (a) is an important component of the lipoprotein particle Lp(a) and shows extensive homology to plasminogen. Lp(a) particles form from the covalent linking of ApoB on LDL particles with Apo(a). Lp(a) particles may play a role in thrombosis. Genetic polymorphisms in the LPA gene encoding apolipoprotein (a) with it increased levels associate with increased risk of atherosclerosis and related morbidity. Many other genes whose products are involved in the turnover of lipoproteins, regulation of inflammatory response, enzymatic metabolism of arachidonic acid, metabolism of homocysteine, cell cycle regulation, synthesis of vasoactive substances by endothelial cells, etc. are candidates for genetic predisposition of some individuals to the fast atherosclerosis development.

Role of most important risk factors in the progression of atherosclerosis is summarized in the Table 2-4.

Table 2-4. Correctable risk factors contribution to the development of atherosclerosis

Risk factor	Mechanism of action
Cigarette smoking	(1) Catecholamine release → ↑fibrinogen level, activation of monocytes, platelets activation; (2) endothelial dysfunction; (3) atherogenic dyslipidemia; (4) oxidative stress.
Arterial hypertension	(1) Endothelial dysfunction; (2) increased proliferation of vascular smooth muscle cells and fibroblasts with elevation media/intima.
Diabetes mellitus	(1) Atherogenic dyslipidemia; (2) glycosylation of proteins with inflammation in the arterial wall; (3) endothe-

	lial dysfunction; (4) hyperinsulinemia (in DM2) which stimulate hypertrophy of arterial media layer.
Atherogenic dyslipoproteinemia	(1) Increased thrombogenic potential of the blood; (2) increased efflux of atherogenic lipoproteins into the vessel wall; (3) stimulation of both local and systemic inflammatory response; (4) endothelial dysfunction.
Hyperhomocysteinemia	(1) Oxidative stress, (2) proliferation of vSMCs; (3) activation of coagulation factor V; (4) inhibition of protein C; (5) ↑ aggregation of platelets; (6) activation of NF-kB with systemic and local inflammation in the vascular wall.
Elevation concentration of serum fibrinogen	(1) ↑ plasma viscosity; (2) ↑ aggregation of platelets; (3) proliferation of vSMCs; (4) inflammation in the vascular wall.
Increase concentration of lipoprotein (a)	(1) Impaired fibrinolysis; (2) delivery of cholesterol at sites of arterial injury; (3) proliferation of vSMCs; (4) increased expression of ICAM-1 in endothelial cells.
Small LDL particle size	1) ↑ ability to cross into the subintimal space; (2) ↑ binding to intimal proteoglycans; (3) high susceptibility to oxidation; (4) reduced affinity to LDL receptor.
Increase concentration of C-reactive protein	(1) ↑ expression of tissue factor and PAI-1 → hypercoagulability; (2) activation of complement; (3) ↓ NO production.
Nephrotic syndrome	(1) ↑ production of lipids and lipoprotein(a) in the liver; (2) thrombophilic state; (3) endothelial dysfunction.
Hypothyroidism	↓ LDLR synthesis in the liver

Pathophysiological basis for prophylaxis and treatment of atherosclerosis and it's clinical complications: (1) healthy lifestyle including healthy diet (low-fat diet to reduce serum cholesterol levels, and a diet with a reasonable amount of calories, carbohydrates and rich in micronutrients, for example, Mediterranean diet), adequate physical activity and refusal of pernicious habits (smoking, excessive alcohol consumption); (2) adequate treatment of diseases accelerating atherogenesis (arterial hypertension, diabetes mellitus, chronic inflammatory diseases); (3) control of serum glucose and cholesterol level; (4) drug therapy including:

- Hydroxymethyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) with pleiotropic effects. They inhibit the endogenous synthesis of cholesterol in the liver and inhibit progression of atherosclerosis by a direct effect on the arterial wall. Statins suppress the synthesis of isoprenoid lipid anchors thus impair signaling pathways through small G-proteins (Ras and RhoA). Statins also induce the expression of the atheroprotective endothelial transcription factors KLF2 and KLF4 and suppress inflammation.

- Drugs inhibiting the reabsorption of bile acids from the gastrointestinal tract thus decreasing cholesterol concentration (cholestyramine).
- Niacin can be used to decrease hepatic secretion of VLDL.
- Antiinflammatory and antithrombotic drugs.

A thrombus that forms over a ruptured plaque can be removed by direct enzymatic lysis. Thrombi may also be removed mechanically using a catheter. The atherosclerotic plaque itself can be removed in some cases using an atherectomy catheter or by an open surgical procedure known as endarterectomy. An acutely occluded vessel can be opened using a balloon angioplasty. If catheter-based methods are not successful, patients with severe atherosclerotic coronary artery disease can also undergo coronary artery bypass grafting.

Ischemic (coronary) heart disease (IHD, CHD)

Before discussion of etiology and pathogenesis of IHD it is necessary to remember basic postulates describing normal coronary blood flow and energy production in the myocardium:

- Myocardial oxygen extraction is high in the basal state (approximately 75% at rest and 90% during ischemia) and adaptation of the heart to the increased demand is achieved mainly through vasodilatation of coronary resistance arteries.
- Coronary arteries have a good ability to autoregulate. Autoregulation is a phenomenon characterized by the ability to maintain relatively constant blood flow in a certain range of perfusion pressure (due to constriction of vSMCs in response to elevation of perfusion pressure and relaxation of vSMCs when perfusion pressure falls).
- Coronary perfusion of the left ventricular is maximal during diastolic phase when wall tension and coronary resistance are lowest.
- Intramural gradient in tension is higher in the subendocardial layers, so, subendocardial layers of the myocardium are more susceptible to ischemia.

Ischemic heart disease includes several forms of pathology:

1. Sudden coronary death.
2. Angina pectoris.
3. Myocardial infarction.
4. Cardiac arrhythmias.
5. Heart failure.

Etiology of ischemic heart disease: atherosclerotic lesion of coronary arteries (in most cases), coronary vasospasm, inflammation of coronary arteries, thromboembolism of coronary arteries (in patients with infective endocarditis) and malformations of coronary arteries. Main link of pathogenesis of IHD is myocardial ischemia, which is resulted from imbalance between inadequate coronary blood flow and increased myocardial oxygen demand.

Sudden coronary death results from fatal arrhythmia complicated ischemia. Pathogenesis of arrhythmias related to ischemia will be discussed later. Post-

mortem examination reveals high-grade coronary stenosis and commonly left ventricular hypertrophy.

Angina pectoris

Angina pectoris manifests as chest pain or equivalents, caused by myocardial ischemia. Different forms of angina were described. Classical (exertional) angina is provoked by physical activity, cold environment and meals. Decubitus angina occurs when the patient is lying down (at rest). Variant (Prinzmetal's) angina starts without any provocation, usually at rest, as a result of coronary artery vasoconstriction. Unstable angina is an angina that appears for the first time (with duration less than 1 month), or worsening angina, or angina at rest.

Angina can be subdivided pathophysiologically into demand angina and supply angina. Demand angina is caused by an increase in myocardial oxygen requirements and workload and the inability to provide adequate blood supply. Physical and emotional activity, fever, thyrotoxicosis, anemia, tachycardia and hypoglycemia are main factors provoking demand angina. Ischemia firstly affects subendocardial layers of the myocardium. Demand angina leads to decreasing of the left ventricle compliance. This type of angina requires β-blockers and heart rate-limiting calcium antagonists for its treatment.

Supply angina results from decreased oxygen delivery to the myocardium. It may be stable and unstable. Supply angina results in increasing of left ventricle compliance. Treatment of supply angina requires coronary vasodilators (nitrates, calcium antagonists). Coronary artery obstruction is the primary cause of supply angina. There are two types of the coronary obstruction: fixed and dynamic.

- Fixed coronary obstruction results from stenosis of coronary artery by atherosclerotic plaque. Different degree of fixed coronary obstruction leads to different clinical signs of angina (Fig. 2-7).

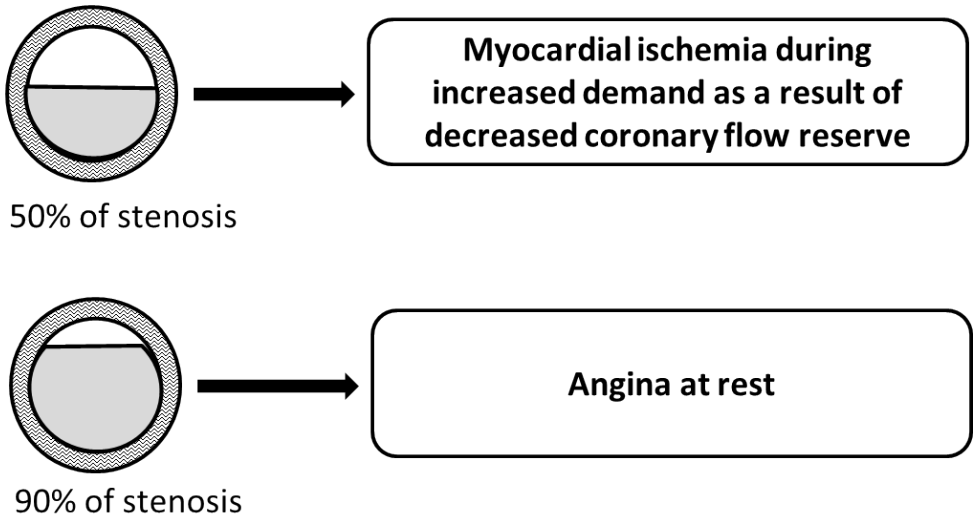


Figure 2-7. Fixed coronary stenosis

- Dynamic coronary obstruction caused by coronary vasoconstriction or thrombosis of coronary artery. Dynamic component of coronary obstruction may lead to ischemic episodes even during hemodinamically insignificant coronary stenosis. Such situation is common in endothelial dysfunction, which is characterized by predomination of vasoconstrictors' effects and loss of athrombogenic surface.
- Coronary steal phenomenon may be intracoronary or intercoronary. It is schematically represented in the Fig. 2-8.

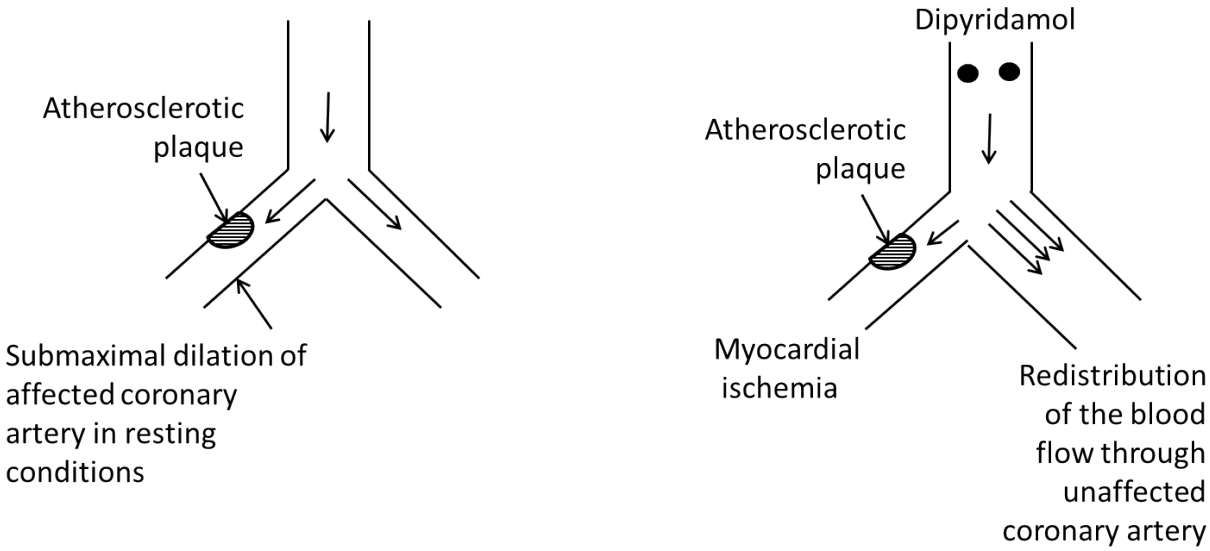


Figure 2-8. Coronary steal phenomenon

During resting conditions coronary arteries narrowed by atherosclerotic plaques are in the state of maximal dilation. Unaffected coronary arteries have a significant coronary dilating reserve. Exposure of some drugs (dipyridamol, nitroprusside, hydralazine or inhaled anesthetic isoflurane), physical exercises or anatomical causes (new patterns of collateral vessels growth or formation of arteriovenous fistula as a complication of myocardial infarction) lead to dilation of unaffected coronary artery. This "shunting" creates more ischemia of the myocardium receiving blood from the narrowed coronary artery.

Some patients, especially females with positive history of angina and positive exercise test may demonstrate, angiographically, normal coronary arteries. Such situation is called as **"cardiac syndrome X".** Myocardial ischemia in these patients reflects inadequate dilator response of the coronary microcirculation rather than stenosis of main coronary arteries.

In general, consequences of acute myocardial ischemia in the absence of collaterals are summarized in the Fig. 2-9. They depend on duration of ischemia, type of occluded coronary artery, functional state of the heart, development of collateral vessels, and many other factors (See section "Ischemia" in the Textbook "General Pathophysiology: the essentials").

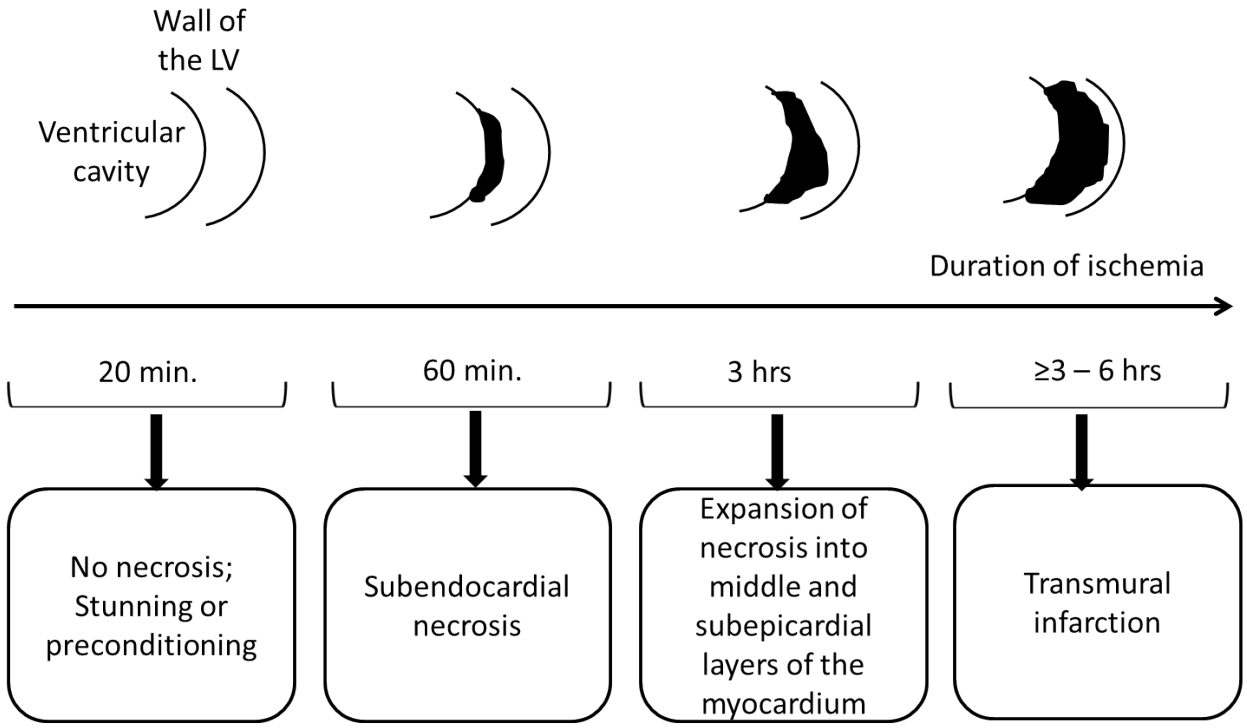


Figure 2-9. Outcomes of acute ischemia in the absence of collaterals
(according with Eu. Braunwald, 2007, with modifications)

Prolonged **irreversible myocardial ischemia** leads to the inhibition of oxidative phosphorylation, severe ATP deficiency and activation of glycogenolysis and anaerobic glycolysis (See universal molecular mechanisms of cellular injury in the Textbook "General pathophysiology: the essentials"). Accumulation of Na^+, lactate, H^+, Ca^{2+}, purines results in osmotic swelling of cardiomyocytes, loss of membranes integrity, activation of lyzosomal enzymes and irreversible necrotic death of cardiomyocytes. In the presence of collateral blood flow, cardiomyocytes begin to take free fatty acids. Disbalance between their consumption and utilization results in the accumulation of free fatty acids, acyl-KoA and acylcarnitine, which are able to damage mitochondria and sarcolemma of cardiomyocytes. Despite the fact that most part of cardiomyocytes during severe ischemia die from necrosis, other forms of cell death (apoptosis and autophagy) may play a significant role in the spreading of zone of died cardiomyocytes. Necrosis results in inflammatory reaction combined with secondary injury. Pathogenesis of irreversible injury of the myocardium following critical ischemia is illustrated in the Fig. 2-10.

Disruption of the vulnerable atherosclerotic plaque by proteolytic enzymes released from activated macrophages with subsequent exposure of tissue factor triggers activation of platelets, thrombosis and coronary vasoconstriction. These pathologic events play an important role in the pathogenesis of **acute coronary syndrome.** Acute coronary syndrome includes unstable angina and myocardial infarction.

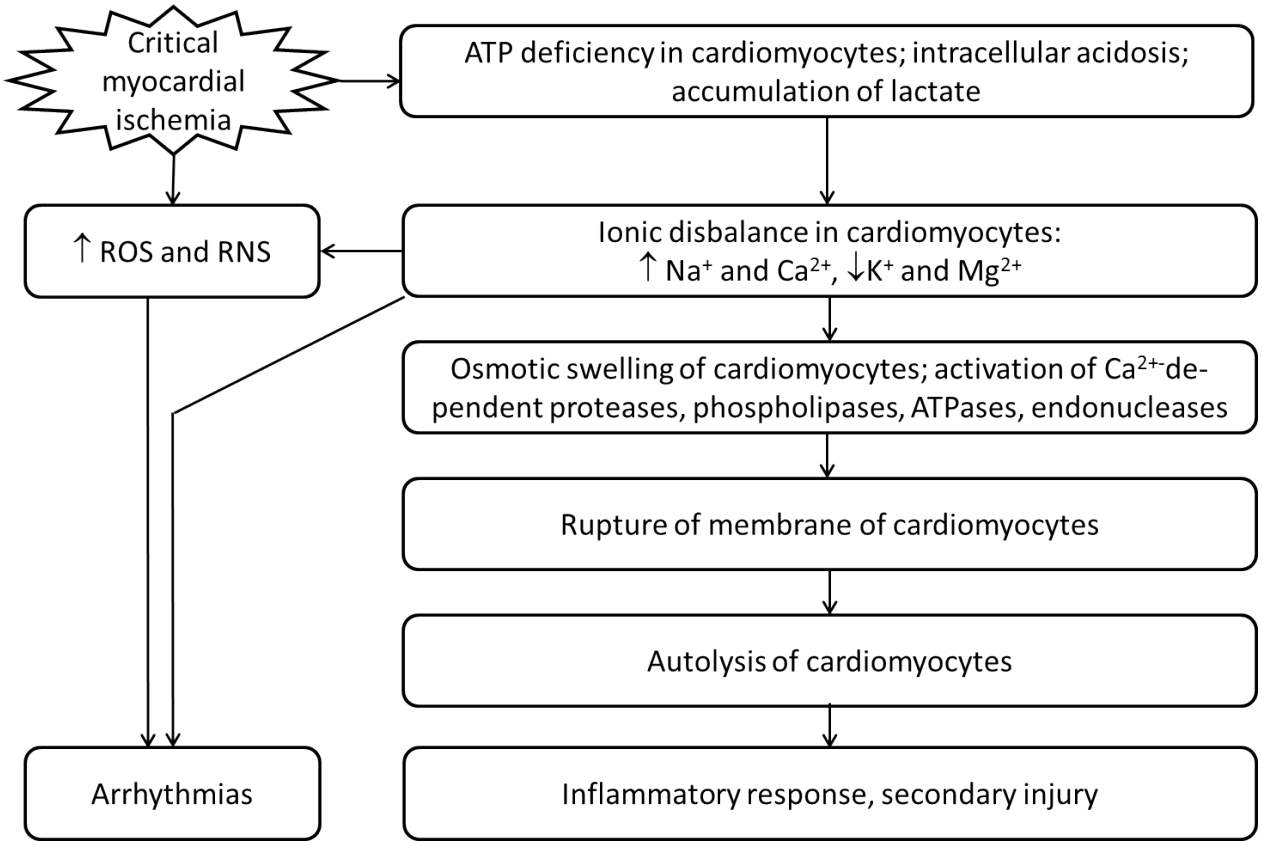


Figure 2-10. Pathogenesis of irreversible ischemic myocardial injury

Myocardial infarction

Myocardial infarction is a myocardial ischemic necrosis. Despite the fact that coronary obstruction and thrombosis is a leading cause of myocardial infarction, other rare causes such as coronary embolism, congenital coronary abnormalities, coronary vasospasm and inflammatory diseases affecting coronary arteries may lead to the myocardial infarction. Almost all myocardial infarctions affect the left ventricle. Myocardial infarction is characterized by the triad of signs: (1) ischemic-type chest pain or discomfort; (2) elevated serum cardiac markers and (3) specific ECG abnormalities. Mechanisms of ischemic cardiac pain can be simplified as following: ischemia → switching to the anaerobic metabolism → accumulation of metabolites and ions (adenosine, lactate, H^+, K^+ etc.) → chemical and mechanical stimulation of sensory afferent nerves ending in the coronary vessels and myocardium from 1^{st}-4^{th} thoracic spinal nerves → ascending of impulses via spinal cord to the thalamus → activation of the cerebral cortex → pain. Elevation of serum cardiac markers is resulted from the destruction of membranes of cardiomyocytes with their irreversible injury and releasing of specific proteins from cardiomyocytes, for instance, most indicative troponins T and I and myoglobin isoenzyme of creatine kinase (CK-MB). Troponins are cardiac-derived sarcomeric proteins. Their level increases firstly 2-4 hours after infarction; peak reaches to 10-24 hours and persists during 5-14 days. CK-MB levels rise within 4-8 hours and persist dur-

ing 48-72 hours after infarction. In contrast, patients' blood serum with unstable angina doesn't demonstrate elevated cardiac markers.

Based on specific ECG changes myocardial infarction can be subdivided into infarction with ST-elevation (STEMI) and non-ST-elevation myocardial infarction (NSTEMI). Patients with NSTEMI have elevated serum cardiac markers, but no any ST elevation on the ECG. The fragment of patient's ECG with STEMI is presented below (Fig. 2-11).

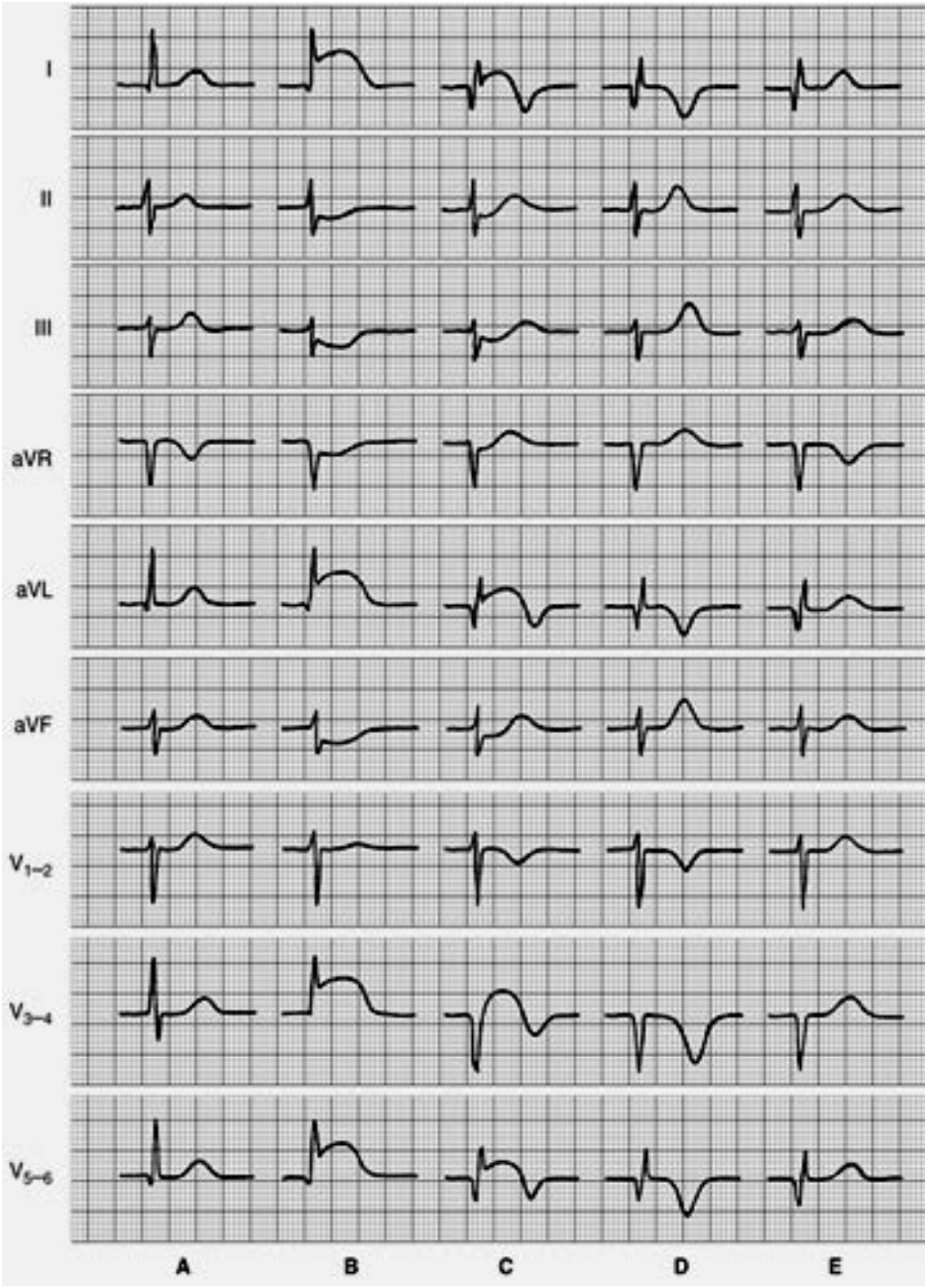


Figure 2-11. ECG of patient with STEMI with elevated serum cardiac markers

A – normal ECG, B – early phase (1 hour following infarction), C – changes following several hours to days after infarction, D – changes following several days to weeks after infarction, E – changes following months-years after infarction.

ECG changes in STEMI differ during stages. In early acute stage changes of T wave is observed: T wave becomes tall and symmetrically narrow, with its inversion following a few hours. Abnormal T wave reflects myocardial ischemia. During evolved acute phase ST segment elevation occurs. It illustrates ischemic injury. Pathologic Q wave (deep and/or wide) appears several hours or days after necrosis and reflects irreversible myocardial cell death (necrosis). Pathologic Q wave tends to persist for the lifetime of affected patient reflecting postinfarction scar formation. Not all myocardial infarctions lead to pathologic Q wave. Absence of pathologic Q wave and detection of cardiac markers of irreversible myocardial injury indicate not transmural, but subendocardial infarction (so-called non-Q wave infarction). It was found that patients with non-Q wave infarction had lower initial mortality, but higher risk of repeated infarction and higher later mortality.

Myocardial infarction may lead to different complications (Table 2-5).

Pathophysiologic basis for the treatment of myocardial infarction: (1) adequate analgesia with narcotic analgesics to relieve pain, which activates SNS and negatively influence on the coronary and systemic hemodynamic; (2) antithrombotic drugs including antiplatelet drugs and anticoagulants; (3) antianginal drugs; (4) invasive methods, if possible - coronary angioplasty with subsequent revascuarization or percutaneous coronary intervention to restore coronary blood flow; (6) if invasive methods are found impossible, pharmacological thrombolysis (fibrinolysis) is recommended (See the Textbook "General pathophysiology: the essentials); (7) prevention and treatment of complications.

Table 2-5. Pathophysiologic characteristic of complications of the myocardial infarction

Complications	General characteristic
Cardiogenic shock	Occurs after necrotic death of at least 40% of cardiomyocytes. Resulted from decreased cardiac output. See the Textbook "General pathophysiology: the essentials".
Arrhythmias	The most common complications of myocardial infarction. They may be caused by ischemia, acidosis, sympathetic stimulation and electrolyte imbalances. Ventricular arrhythmias may lead to sudden death.
Heart failure	Develops when the infarction affects 20-25% of the cardiomyocytes in the left ventricle. Scar also impairs myocardial contractility and motion of the myocardial wall.
Thromboembolic complications	Mural thrombi form on the damaged endocardium. Portions of such thrombi may break off and cause thromboembolism with blockage of arteries in the brain, kidneys, spleen, intestine or extremities.
Acute mitral valve regurgitation	Resulted from the rupture or dysfunction of dying from necrosis papillary muscles with volume overload of the left atrium with subsequent pulmonary edema.
Rupture of the my-	Most frequently develops between 2^{nd} and 10^{th} days after in-

ocardium	farction. Rupture of any portion of the ventricular wall leads to the cardiac tamponade. Post-infarction septal rupture causes left-to-right intracardiac shunting of the blood.
Postinfarction pericarditis	Fibrinous pericarditis may develop soon after infarction. Total resolution of exudate or formation of fibrous adhesions may occur. Autoimmune pericarditis with pericardial effusion and fever is termed as a Dressler's syndrome. The last may develop following 2 weeks to several months after infarction.
Ventricle aneurysm	It is a late complication and characterized by the formation of a thin fibrous scar with progressive deformation of the external cardiac surface. Abnormal ventricle contraction and slowing of the blood flow in affected ventricle leads to the formation of mural thrombi with increasing of the risk of thromboembolic complications.

Reperfusion injury

Early restoration of diminished blood flow (with surgical methods of revascularization or pharmacological thrombolysis) influences positively on the recovery of myocardial contractility and reduces overall mortality from myocardial infarction. However, **reperfusion injury** may develop after restoration of coronary blood flow in the myocardium with irreversibly injured cardiomyocytes. Main hallmarks of reperfusion injury are:

- Expansion of infarction area;
- Development of so-called reperfusion arrhythmias.

Basic events leading to reperfusion injury are summarized in the Fig. 2-12.

"No-reflow" phenomenon

Sometimes (up to 50% of revascularization cases) restoration of coronary flow can't lead to normal myocardial perfusion due to post ischemic microcirculatory abnormalities. This phenomenon is called "no-reflow" phenomenon. Basic mechanisms of such phenomenon are: (1) damage of coronary endothelial cells, their swelling, degradation of glycocalix, expression of adhesion molecules and attachment of activated leukocytes to the endothelium; (2) formation of "plugs" from activated leukocytes, red blood cells and platelets; (3) compression of microcirculatory vessels by swelling cardiomyocytes; (4) microcirculatory vasoconstriction caused by vasoconstrictors released from endothelial cells, activated platelets and neutrophils; (5) microembolization of microcirculatory vessels with fragments of destroyed atherosclerotic plaque following invasive revascularization. Antiembolic approaches and pharmacotherapy including cardioprotectors, antithrombotics, vasodilators, control of glycaemia help to prevent or correct no-reflow phenomenon.

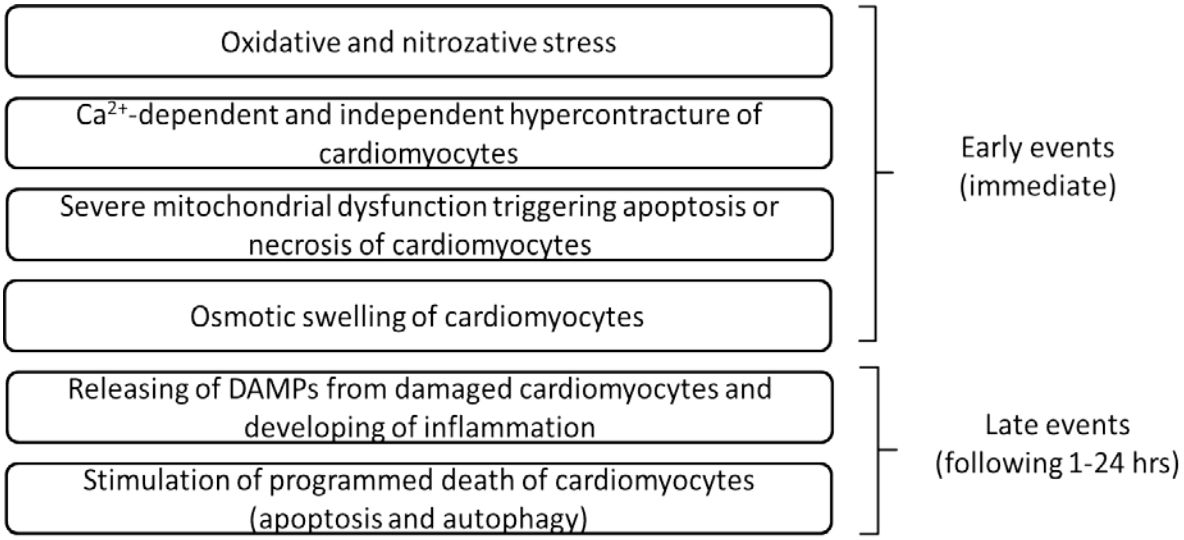


Figure 2-12. Pathogenesis of irreversible reperfusion injury

Reversible myocardial ischemia may lead to:

A. Preconditioning or postconditioning.
B. Hibernating myocardium.
C. Stunned myocardium.

Preconditioning is a protective mechanism directed against irreversible injury of cardiomyocytes. Brief episodes of reversible ischemia before prolonged coronary occlusion will reduce necrosis of cardiomyocytes. Mechanisms of preconditioning were discussed in the Textbook "General pathophysiology: the essentials". Postconditioning occurs, when intermittent ischemia or pharmacological antagonists during reperfusion protect cardiomyocytes.

Hibernating myocardium is a stable, potentially reversible adaptive depression of myocardial contractility caused by myocardial hypoperfusion. Biological significance of this adaptive reaction contributes to the coordination of myocardial oxygen demand and myocardial contractility. Restoration of coronary blood flow before irreversible ultrastructural changes in cardiomyocytes may reverse hibernation of the myocardium. Hibernation may be acute or chronic. Acute hibernation results from disorders of calcium entering in the sarcoplasmic reticulum and loss of myofibrils sensitivity to calcium ions. Continuous myocardial hypoperfusion (for instance, in patients with chronic ischemic heart disease) is accompanied by chronic hibernation. Structural and functional changes of cardiomyocytes during chronic myocardial hibernation include: (1) decreased cytoskeletal and contractile proteins; (2) increased expression of heat shock proteins, especially Hsp 70, HIF and VEGF; (3) metabolic reprogramming of cardiomyocytes, increase glucose utilization as a main source of energy instead of free fatty acids and accumulation of glycogen; (4) gaining of fetal phenotype; (5) decreased number of mitochondria and their ultrastructural changes; (6) decreased sympathetic innervation of hibernating myocardium; (7) apoptosis of separate cardiomyocytes and microautophagy. Timely revascularization helps to correct hibernation adequately.

Stunned myocardium is characterized by a depressed myocardial contractility despite normal myocardial perfusion. Areas of stunned myocardium may coexist with irreversibly damaged myocardium and contribute to improvements in myocardial contractility with time after myocardial infarction. Stunned myocardium may develop following reperfusion of the myocardium. Basic pathogenetic events leading to stunned myocardium are oxidative stress and nitrozative stress. Firstly, excessive concentrations of ROS and RNS suppress activity of Na^+/K^+-ATPase with accumulation of Na^+ in cardiomyocytes with subsequent activation of Na^+/Ca^{2+}-exchanger. The latter facilitates intracellular Ca^{2+} accumulation with a subsequent activation of calcium-dependent enzymes calpains and degradation of contractile proteins and proteins regulating their activity. Secondly, excessive concentrations of ROS and RNS impair sensitivity of miofilaments to Ca^{2+}. Thirdly, ROS and RNS impair functional activity of the sarcoplasmic reticulum in cardiomyocytes with alteration of calcium cycling in these cells. Restoration of the disbalance between coronary blood flow and myocardial contractility requires time from days to weeks.

Arrhythmias

Arrhythmias are changes of normal rate, regularity, origin of cardiac excitation or disorders of spreading of excitation resulting in abnormal relationship or sequence of atriums and ventricles excitation and contraction.

To better understanding of etiology and pathogenesis of arrhythmias it is necessary to know basic principles of electrophysiology of the heart. Sinoatrial node (SA node) is a main pacemaker rhythmically generating impulses with frequency 60-100 impulses per minute in adult healthy individuals. Ability to generate impulses is resulted from spontaneous diastolic depolarization in pacemaker cells. Then impulse travels through the atrioventricular node (AV node) to the atrioventricular bundle, or bundle of His, which branches into left and right branches and terminates at the Purkinje fibers sending impulse to the cardiomyocytes. The AV node and other portions of the conduction system can, in abnormal situations, become the cardiac pacemaker. In addition, diseased atrial and ventricular muscle fibers can have their membrane potentials reduced and discharge repetitively.

Myocardial fibers have a resting membrane potential of approximately –90 mV. Despite the fact that the individual fibers are separated by membranes, depolarization wave spreads radially through them because of the presence of gap junctions. The transmembrane action potential of a cardiac muscle cells is characterized by the following phases (Fig. 2-13): rapid depolarization (phase 0), an initial rapid repolarization (phase 1), a plateau (phase 2), and a slow repolarization (phase 3) that allows return to the resting membrane potential (phase 4). The initial depolarization is resulted from Na^+ influx through rapidly opening Na^+ channels (the Na^+ current, I_{Na}, Fig. 2-13, A and B). The inactivation of Na^+ channels relates to the rapid repolarization phase (Fig. 2-13, C). Ca^{2+} influx through more slowly opening Ca^{2+} channels (the Ca^{2+} current, I_{Ca}) produces the plateau phase (Fig. 2-13,

D), and repolarization is due to net K^+ efflux through multiple types of K^+ channels (Fig. 2-13, E).

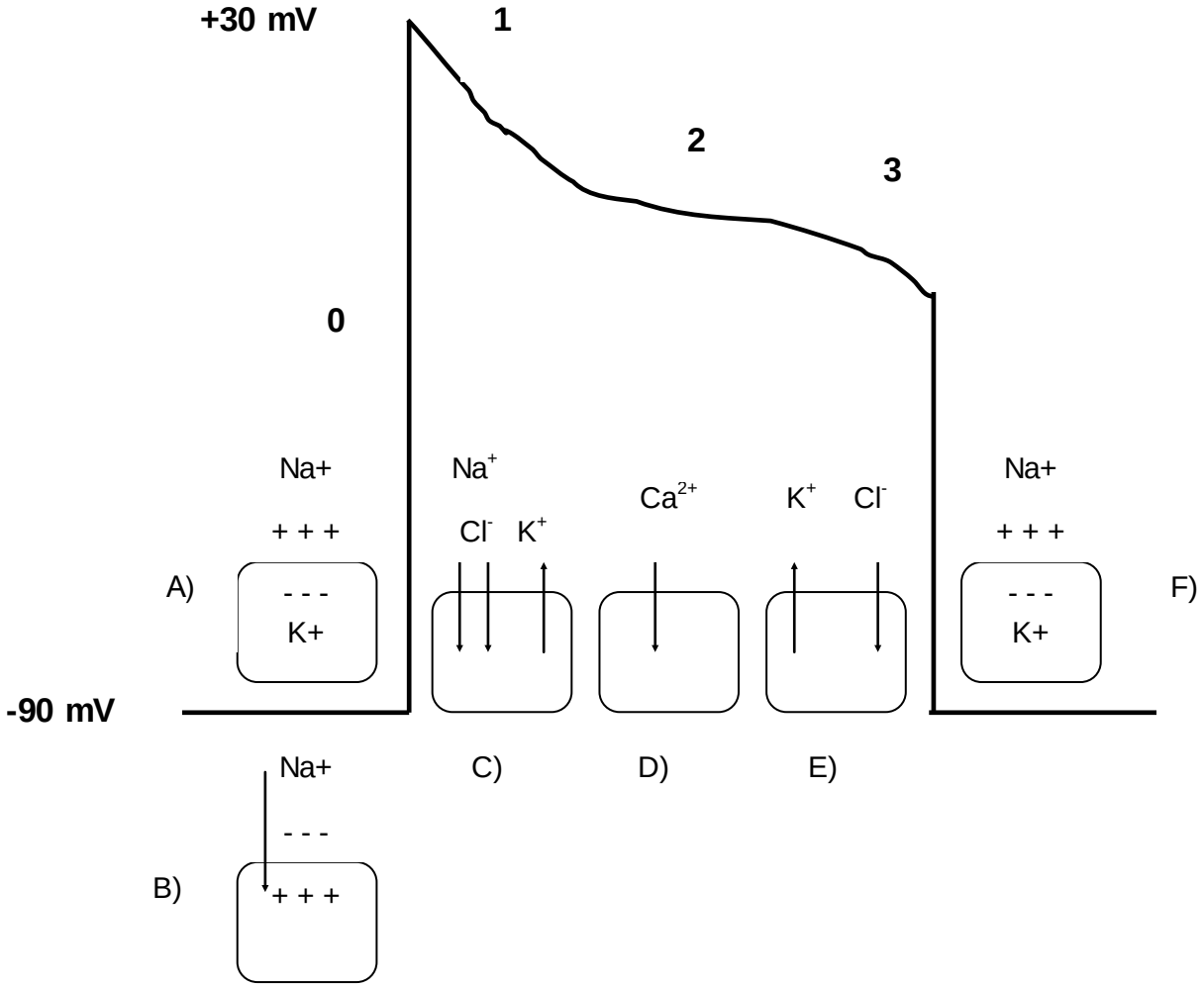


Figure 2-13. Schematic representation of the action potential in the ventricular cardiomyocytes

The potential in the cells of the sinus node is a pacemaker potential (Fig. 2-14). The most negative value of the resting potential is called maximal diastolic potential. It rises steadily until the threshold potential (– 40 mV) is reached once more and an action potential is again formed. Beginning with the maximal diastolic potential nonselective conductance is increased and influx of cations into the cell leads to slow depolarization. Once the threshold potential has been reached, Ca^{2+} now rises relatively rapidly, the potential rising more steeply so that an increased influx of Ca^{2+} produces the upstroke of the action potential. While the potential overshoots to positive values, leading to an outward K^+ flux, the pacemaker cell is again repolarized to the maximal diastolic potential. Each action potential in the sinus node normally results in a heartbeat, i.e., the impulse frequency of the pacemaker determines the rate of the heartbeat. Heart rate is increased by the activity of sympathetic influences on the sinus node (i.e. positive inotropic effect mediated via β1-adrenoreceptors) and decreased by parasympathetic, muscarinic fibers (i.e. neg-

ative chronotropic). This is due to changes in the slow depolarization rise and altered maximal diastolic potential in the sinus node.

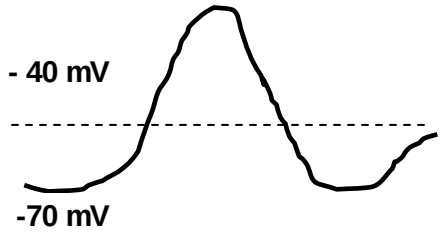


Figure 2-14. Schematic representation of the action potential in pacemaker cells in the sinus node

Etiology of arrhythmias is following:

- Disorders of neural and humoral cardiac regulation.
- Diseases of central and vegetative nervous system.
- Diseases affecting the myocardium with injury of cardiomyocytes and conducting system of the heart (rheumatic heart disease, cardiac malformations, valvular heart diseases, ischemic heart disease, myocarditis, cardiomyopathies, intoxications, tumors, etc.).
- Inborn anomalies of conducting system in the heart.
- Disorders of water and electrolyte balance and acid-base disorders.
- Reflexes from large blood vessels and viscera.
- Age-dependent changes in the heart, which are characterized by a decrease number of pacemaker cells in the sinus node and AV-node coexisting with alterations in the myocardium and changes of metabolism of cardiomyocytes.
- Exposure of cardiotoxins and drugs with arrhythmogenic properties.

There are three basic mechanisms of arrhythmias development:

1. Disorders of impulses formation.
2. Disorders of impulses propagation.
3. Combination of abnormal impulses formation and propagation.

1. Arrhythmias due to abnormal impulses formation may be resulted from: (a) alteration of impulses formation in the sinus node, but it stays a main pacemaker (sinus tachycardia, sinus bradycardia, sinus arrhythmia); (b) arrhythmias due to abnormal automaticity; (c) arrhythmias caused by trigger activity. Let us consider them in detail.

Sinus bradycardia is characterized by a decrease frequency of impulses generation in the sinus node with subsequent decrease in heart rate less than 60 beats per minute (Fig. 2-15). Sinus bradycardia may be resulted from predomination on nervus vagus activity in athletes or in patients with parasympathetic nervous system dysautonomy. Parasympathetic hyperactivation is seen in neurosis, vagoinsular crisis, intracranial hypertension and some somatic diseases with reflex-mediated vagus activation. Different alteration of pacemaker cells in the sinus node

(following hypothermia, food starvation, metabolic alkalosis, hyperkalemia, hypercalcemia, hyperoxia, hypopituitarism, hypothyroidism, uremia, liver failure, obstructive jaundice, Gram-negative sepsis, typhoid fever, diseases of the myocardium) may also result in the sinus bradycardia. Some drugs (antiarrhythmic, cardiac glycosides, tranquilizers, some antihypertensives and others) may affect sinus node activity. Rare familial form of the constitutional sinus bradycardia was described.

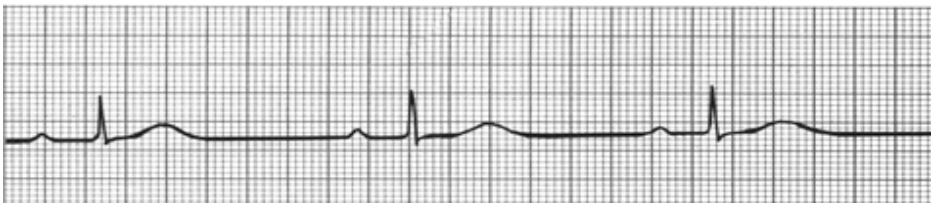


Figure 2-15. ECG fragment with sinus bradycardia

Mechanism of sinus bradycardia mediated by vagus activation is following: acetylcholine released from nerve ending stimulates permeability of pacemaker membranes for the K^+ ions. Maximal diastolic potential of cells in SA-node becomes more negative. The time for threshold formation increases. Activation of vagus also delays conduction in the AV-node. As a result, heart rate decreases. Hemodynamic disorders during sinus bradycardia results from inadequate cardiac output, especially its brain fraction. Sinus bradycardia during extremal states associates with poor prognosis.

Sinus tachycardia is characterized by an increase of heart rate more than 100 beats per minute (Fig. 2-16) resulted from more frequent generation of impulses in the SA-node.

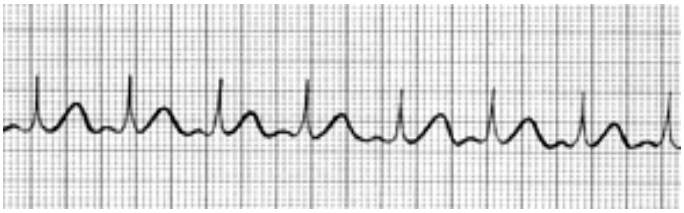


Figure 2-16. ECG fragment with sinus tachycardia

Such abnormal activity of main pacemaker cells may be mediated via hyperactivation of the sympathetic nervous system during physical exercises, emotional stress, acute hemorrhage, fever, pain, hypoxemia, acidosis, hypoglycemia, alcohol abuse, overdose of some drugs (sympathomimetics, glucocorticoids, antihypertensives, diuretics) and pheochromocytoma. Dysautonomy of the vegetative nervous system may be a cause of such arrhythmia. Catecholamines stimulate entry of Na^+ and Ca^{2+} thus making maximal diastolic potential less negative. Threshold potential is gained faster, with subsequent acceleration of both impulses formation and propagation. Organic damage of pacemaker cells (which is seen in myocarditis, myocardial dystrophy) or their functional disorders due to ionic disbalance may lead to sinus tachycardia as well. Hyperthyroidism also often manifests by differ-

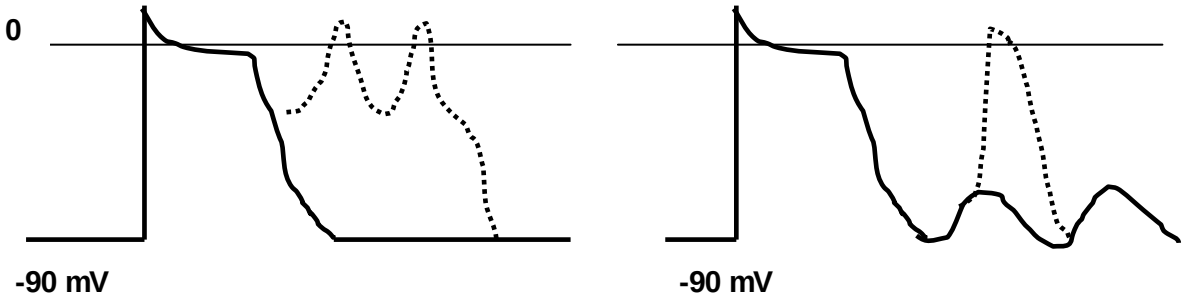
ent tachyarrhythmias. Biological significance of sinus tachycardia is differing: on the one hand, it reflects compensatory reaction which helps to preserve cardiac output in extremal states; on the other hand, it increases myocardial oxygen demand and leads to the shortening of the diastole thus predisposing to the myocardial ischemia.

Sinus arrhythmia is an alternation of more frequent and slower sinus rhythm. It may be phasic (slower rhythm during exhalation and more frequent during inhalation, which is common in children and adolescents) and non-phasic, due to functional, vegetative nervous system-mediated abnormalities in pacemaker cells in aging persons during their falling asleep and arousal or due to structural changes of cells in SA-node.

Arrhythmias due to abnormal automaticity are caused by an impaired function of main pacemakers and activation of secondary pacemakers in the AV-node, His bandle or even in the myocardium. These types of arrhythmia include wandering of the atrial pacemaker, initiation of ectopic pacemaker activity (so-called heterotopic arrhythmias) and arrhythmias due to trigger activity (mediated by postdepolarizations.

Normally there is no any spontaneous depolarization in the working cardiomyocytes. However, if resting membrane potential of cardiomyocytes will become less negative, for example, from –70 to –30 mV, this allows to spontaneous diastolic depolarization. Thus, value of resting membrane potential of cells of Purkinje fibers at approximately –50 mV associates with impulses generation in these cells with frequency 150-200/min. Arrhythmia may develop, if frequency of impulses generation by ectopic pacemakers will become more than frequency of impulses generation by cells in SA-node. Different mechanisms may lead to the abnormal spontaneous diastolic depolarization in working cardiomyocytes: (1) disparity of activation and inactivation of K^+ channels; (2) calcium-mediated activation of inward K^+ current; (3) predomination of the Na+ influx in cardiomyocytes (as a consequence of ATP deficiency following profound hypoxia or after cardiac glycosides poisoning).

Trigger activity is a result of postdepolarizations, which may be early or late. Postdepolarizations are in fact oscillations in membrane potential after peak of the action potential (Fig. 2-17). Postdepolarizations prolong duration of action potential.



A) B)

Figure 2-17. Early (A) and late (B) postdepolarizations

For the appearance of a triggered activity three main conditions are necessary: (1) significant depression of the SA-node activity; (2) impairment of impulses propagation from the SA-node; (3) frequency of generation of action potentials by abnormal pacemakers should be higher than by pacemakers in the SA-node.

Early postdepolarizations develop during "plateau" of the action potential (when membrane potential is more positive than -60mV) or during phase 3 of the AP. Formation of repeated peaks of AP is abrogated only after returning of the AP to the resting level. Early postdepolarizations might be founded in the cells of Purkinje fibers and ventricular cardiomyocytes in the midmyocardium (M-cells). Two basic mechanisms are responsible for the development of late postdepolarizations: (1) slowing of the repolarization caused by an increase of inward K^+ or rarely - Na^+ and Ca^{2+} current; (2) decrease of outward K^+ current. Early postdepolarizations may initiate tachyarrhythmias in patients **with prolonged QT interval syndrome**. QT interval reflects time between the initiations of ventricular depolarization to the end of its repolarization. Myocardial excitability differs during this period: from complete refractoriness to the relative refractoriness. During the latter untimely extreme impulses can excite myocardium. Such untimely impulses can initiate atrial or ventricular fibrillation, if it will affect cardiomyocytes during so-called "vulnerable period of the heart". Atrial "vulnerable period" corresponds to QRS complex on ECG, ventricular "vulnerable period" coincides with T wave. Thus, the prolongation of QT interval associates with increasing of duration of ventricular repolarization and higher risk for early postdepolarizations, which clinically manifest by ventricular tachyarrhythmias and syncope or sudden death. Syndrome of prolonged QT interval may be inherited (with autosomal dominant or autosomal recessive type of inheritance) or acquired. Inherited forms of the syndrome are resulted from mutations of genes encoding different ion channels. Acquired syndrome of prolonged QT might be initiated by different drugs (epinephrine, some antihistamines, some antibiotics, antibacterial or antifungal drugs, some diuretics, antipsychotic drugs and antiarrhythmics).

Late postdepolarizations are resulted from the accumulation of intracellular Ca^{2+} in the cytosol and/or sarcoplasmic reticulum of cardiomyocytes. Such higher concentration of $[Ca^{2+}]_i$ favors prolonged inward calcium current after formation of the action potential. Late postdepolarizations may be detected following 1-2 days after myocardial infarction in the atrial and ventricular cardiomyocytes, cells of Purkinje fibers, and endocardial cells. Overdose of cardiac glycosides and hypercatecholaminemia also may lead to late postdepolarizations and different tachyarrhythmias with activation of heterotopic pacemakers.

2. Disorders of impulses propagation are due to following mechanisms:

- Decrease of amplitude of action potentials mainly caused by lack of inward Na^+ current with decline in the amplitude of AP during its 0 phase and reduction of axial flow of excitation wave;
- Deceleration of impulses propagation to unexcited cells (for instance, from viable cells of Purkinje fibers to the damaged cardiomyocytes during myocardial infarction);

- Disorders of intercellular electrotonic interactions, which might be seen, if between two potentially excitable sites of the myocardium zone of damaged myocardium (due to local ischemia, accumulation of K^+) is located. Impulses propagation through damaged zone is significantly slower;
- Increase of resistance of gap junctions to the axial flow, which is resulted from accumulation of intracellular Ca^{2+} (following myocardial ischemia or overdose of cardiac glycosides);
- Myocardial anisotropy. Anisotropy reflects differences in the ability of impulses propagation depending on their direction. Because of the number of gap junctions between neighboring cardiomyocytes is greater in the longitudinal direction than in the transversal, resistance to the axial flow is less under impulses propagation in the longitudinal direction. This means that the velocity of impulses propagation is faster in the longitudinal direction. Myocardial fibrosis, which is characterized by excessive deposition of connective tissue in the heart (in aging heart, chronic ischemic heart disease, scar formation after myocardial infarction) may enhance myocardial anisotropy thus leading to abnormal impulses propagation.

Clinically disorders of impulses propagation are characterized by bradyarrhythmias or tachyarrhythmias. Bradyarrhythmias are hallmarks of different conduction blocks, whereas tachyarrhythmias are due to (1) escape beats from pacemakers of non-sinus origin which activate after sinus arrest; (2) re-entry mechanism.

Normally impulses generated in the sinus node propagate along the conduction system with decaying gradient. However, there are different situations favor not to decreasing of excitation wave, but to it recirculation. Such situations create a focus of abnormal electrical activity. Some conditions are required for the development of re-entry (Fig. 2-18): substrate – or excitable myocardium; alternative (additional) pathway of impulses conduction; unidirectional block of conduction; central region, which is unable to conduct impulses, and trigger initiating re-entry (not obligatory condition).

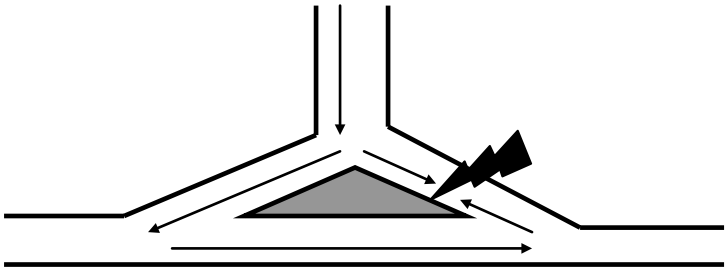


Figure 2-18. Schematic representation of a re-entry loop

Any part of the heart may form a substrate for re-entry. Anatomical re-entry is formed by different morphological structures – Purkinje fibers, accessory conducting pathways, etc. Functional re-entry is most common and is formed by tissues of the heart with different electrophysiological characteristics. For the development of

re-entry, accessorial or alternative conducting pathways must have slower speed of impulses propagation. It occurs, if alternative pathway is longer than main, or if it has less conductance, or this slowing is functional (following tachycardia), or it is caused by morphological injury (due to necrosis of cardiomyocytes or fibrosis), or if it is resulted from an abnormal characteristics of membrane of cardiomyocytes. Unidirectional block of impulses propagation develops, if impulse can't pass in one direction (antegrade, for instance), but it is able to transmit in another direction (retrograde). Re-entry mechanism plays an important role in the initiation of different arrhythmias: paroxysmal supraventricular tachycardia, atrial flutter and atrial fibrillation, ventricular fibrillation and many others.

Pathophysiologic characteristic of selected arrhythmias

Extrasystole (premature beat) is a premature myocardial excitation with premature contraction of the whole heart or some cardiac chambers. Depending on the site of premature impulse formation, they can be subdivided into supraventricular (Fig. 2-19) and ventricular.

Figure 2-19. Fragment of ECG with supraventricular extrasystole

Extrasystoles derived from the single site of premature excitation are monotopic; extrasystoles from various sites of premature excitation are polytopic. Sometimes extrasystoles develop regularly: if the ratio between normal sinus rhythm and premature beat is 2:1, the extrasystoles are determined as bigeminy (Fig. 2-20), if such ratio is 3:1, extrasystoles are called as trigeminy, ratio 4:1 is called as quadrigeminy.

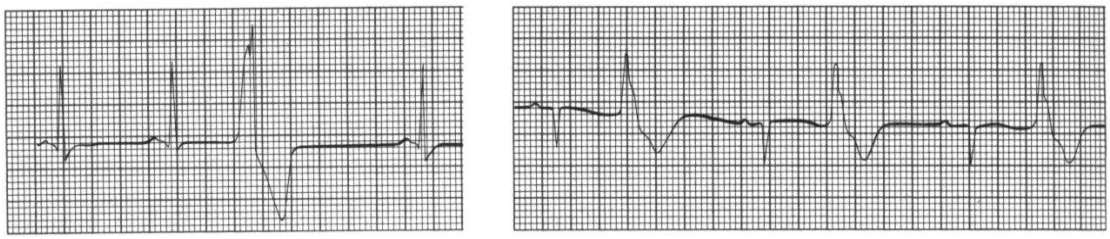


Figure 2-20. ECG characteristic of: A – ventricular extrasystole, B – bigeminy

Extrasystoles may be rare (< 5/min.), intermediate (6-15 /min.), or frequent (>15/min.). Extrasystoles may reflect functional or morphological changes in the myocardium. Rare extrasystoles (less than 30 per hour) may be seen even in healthy individuals. In some cases extrasystoles may be initiated by an irritation of vagal reflexogenic zones, or in contrast, by hyperstimulation of the sympathetic

nervous system (after strong tea, coffee or alcohol consumption, emotional stress, etc). Extrasystoles often coexist with wide range of diseases affecting the heart (acute and chronic coronary heart disease, cardiomyopathies, myocardiodistrophy, myocarditis, pericarditis, cardiac malformations, arterial hypertension and other diseases). Electrolyte disorders and disorders of acid-base equilibrium are also common causes of premature cardiac contractions.

Electrophysiologic mechanisms of extrasystoles involve (1) activation of trigger activity; (2) re-entry. Clinical significance of extrasystoles depends on their frequency. For instance, rare extrasystoles don't lead to any hemodynamic disorders. However, frequent ventricular extrasystoles may predispose to more dangerous arrhythmias, including ventricular fibrillation, and are characterized by a decreasing of stroke volume, and sometimes – cardiac output. Frequent premature beats may decrease duration of diastole thus compromising myocardial coronary blood flow.

Paroxysmal tachycardias involve different tachyarrhythmias with sudden onset. Heart rate may reach to 140-250 beats per minute. Paroxysmal tachycardias may be classified into supraventricular and ventricular (Fig. 2-21). Supraventricular paroxysmal tachycardias are subdivided into atrial and tachycardias from AV-node. Electrophysiological mechanisms of paroxysmal tachyarrhythmias are similar to those observed in extrasystoles, but re-entry mechanism is most common.

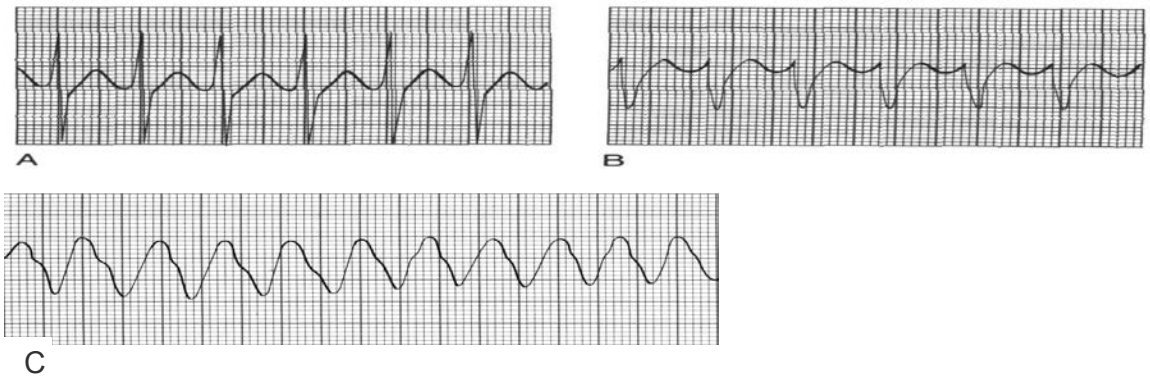


Figure 2-21. ECG during (A, B) supraventricular and (C) ventricular paroxysmal tachycardia

Paroxysmal tachycardia commonly complicates myocardial injury following myocardial infarction, myocarditis, cardiomyopathies, and valvular heart diseases or reflects activation of accessorial conducting pathways. Sometimes supraventricular paroxysmal tachycardia may be initiated by functional causes, such as head rotation or compression of the neck with tight collar. Short-term episodes of paroxysmal supraventricular tachycardia doesn't impair hemodynamic significantly. After it termination some patient may excrete a lot of urine resulted from secretion of natriuretic peptide. In contrast, ventricular tachycardia, especially followed by myocardial infarction, may be life-threatening itself or may be a precursor of ventricular fibrillation. Significant disturbance of hemodynamic in such conditions are resulted from: (1) shortening of diastole and reduction of diastolic filling with sub-

sequent fall in cardiac output and impairment of coronary blood flow with myocardial ischemia and reduction of the myocardial contractility; (2) increasing in myocardial oxygen demand, which together with decreased coronary blood flow exacerbate myocardial ischemia and subsequent impairment of the myocardial contractility; (3) hyperactivation of the sympathetic nervous system resulted from systemic hypoperfusion with subsequent rise of systemic vascular resistance and deterioration of regional blood flow in the skin, muscles, kidneys, liver, gastrointestinal tract, etc.; (4) preexisted heart failure and development of pulmonary edema with hypoxemia and further decreasing of myocardial contractility.

Carotid massage may slow or terminate paroxysmal supraventricular, but not ventricular tachycardia. Antiarrhythmic drugs are necessary for the treatment of paroxysmal tachycardia.

Cardiac fibrillation includes atrial fibrillation and atrial fluttering. They can be paroxysmal or constant. Electrocardiographically atrial fibrillation is characterized by irregular QRS complexes and absence of P wave, but presence of "fibrillation waves" ("f" waves) due to irregular frequent (350-700/min.) contractions of separate atrial cardiomyocytes (Fig. 2-22). Such irregular contraction leads to ineffective atrial contraction and irregular ventricular contractions.

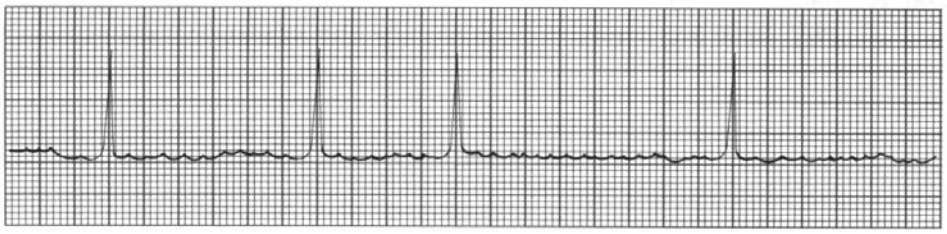


Figure 2-22. ECG fragment during atrial fibrillation

Atrial fibrillation is common form of arrhythmia, taking 2nd place after extrasystoles. Depending on the rate of ventricular contraction, it may be classified into tachysystolic (90-200/min), normosystolic (60-90/min.) or bradysystolic (less than 60/min.). Atrial fibrillation is resulted from underlying pathology: cardiosclerosis, mitral valve disease, cardiomyopathies, thyrotoxicosis, cardiomyopathies, intoxications, pericarditis and many other pathologic conditions including those with electrolyte disorders. Cardiac remodeling with atrial dilation creates a base for atrial fibrillation due to formation of a great number of re-entry loops in such conditions. The latter is a main electrophysiological mechanism of atrial fibrillation. As a rule, at least 4-6 re-entry circuits are formed and supported by an electric heterogeneity of atrial cardiomyocytes, which have distinct effective refractory periods. Asynchronous ventricular contractions are resulted from the blocking of some chaotically generated impulses in the AV-node.

Atrial fibrillation, especially its tachysystolic form, may significantly worse both intracardiac and systemic hemodynamic. Decrease in cardiac output is directly depended on the heart rate: tachycardia associates with decrease and diastolic filling and stroke volume, accordingly. Diminished and/or irregular cardiac output may impair cerebral blood flow, especially in patients with impaired cerebral auto-

regulation. Thus, patients with atrial fibrillation have higher risk of ischemic stroke and thromboembolic complications due to turbulent blood flow in the atria or atrial blood congestion caused by ineffective systolic contraction of atria (2nd component of the Virchow's triad).

Atrial fluttering is characterized by irregular their contraction with rate 200-400/min. It may be paroxysmal or constant. ECG-changes include F-waves and functional blocking of impulses conduction in the AV-node (Fig. 2-23).

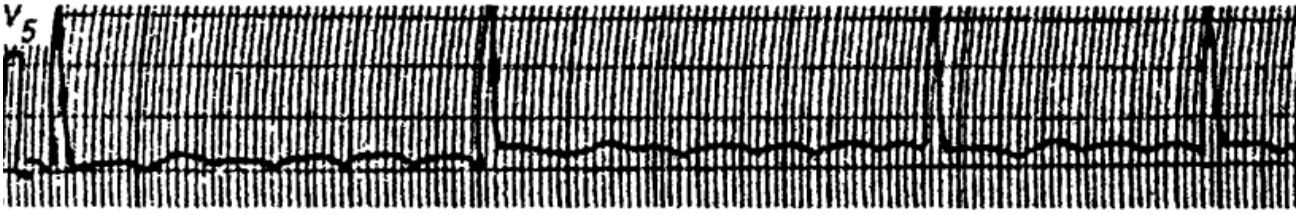


Figure 2-23. Atrial fluttering

Electrophysiological mechanisms and clinical features are similar those which were discussed above, however, with lower risk of thromboembolic complications and lower decrease in cardiac output, compared with atrial fibrillation.

Ventricular fibrillation is a life-threatening arrhythmia, which is characterized by a frequent (200-500/min.), irregular, chaotic contraction of separate cardiomyocytes with critically fall in cardiac output and sudden death. The ECG is presented as an irregular rhythm without organized ventricular complexes (Fig. 2-24).

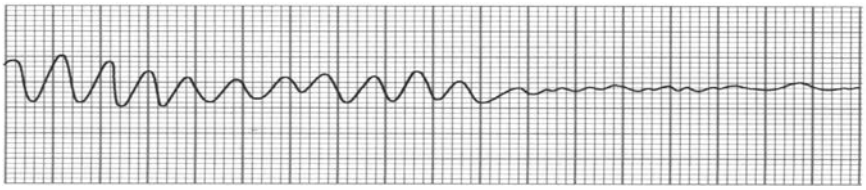
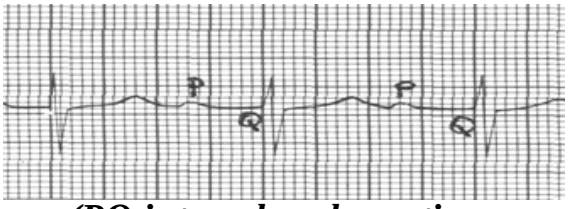


Figure 2-24. Paroxysmal ventricular tachycardia followed to ventricular fibrillation

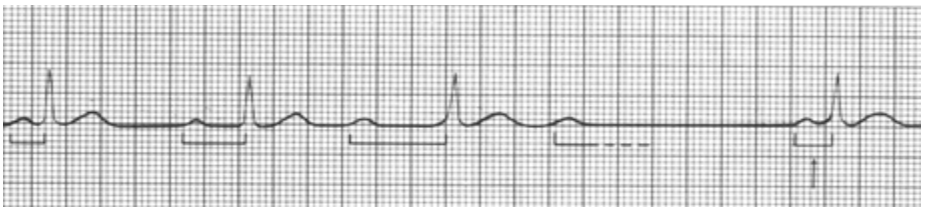
Ventricular fibrillation may develop in patients with IHD, especially myocardial infarction, myocardial hypertrophy and cardiomegaly, cardiomyopathies, some conduction blocks, electrical trauma, cardiac glycosides, anthiarrhythmics and anesthetics overdose, during hypothermia, as a result of terminal states during severe internal diseases, during shock, etc. Mechanism of "re-entry" is a basic electrophysiological mechanism of ventricular fibrillation. As a rule, several micro-"re-entry" persist in the myocardium and create its electrical heterogeneity with an inability to spontaneous termination of impulses recirculation. Clinically ventricular fibrillation manifests as a clinical death resulted from absence of an effective pumping of the blood in the aorta and pulmonary arteries. Absence of resuscitation or ineffective resuscitation leads to the transition of the clinical death into biological death (6-10 min.). Electrical defibrillation and cardiopulmonary resuscitation are basic principles of the ventricular fibrillation management.

In contrast to the ventricular fibrillation, ventricular flutter is characterized by an irregular contraction of ventricular cardiomyocytes with frequency 200-300/min. Electrophysiological mechanism and clinical picture of the ventricular flutter are similar to those in ventricular fibrillation.

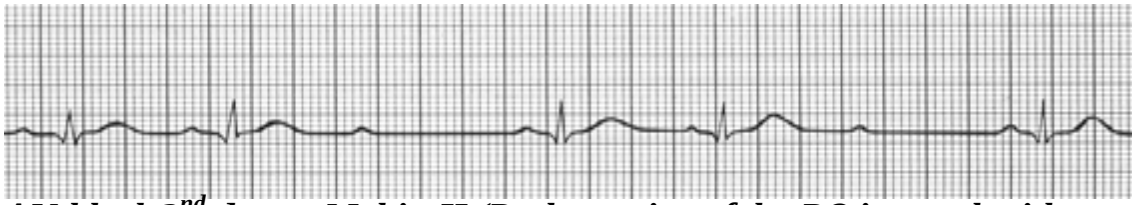
Heart blocks can be classified into sinoatrial block (SA-block), atrioventricular block (AV-block), His bundle block and Purkinje fibers block (Fig. 2-25). Heart blocks result in different forms of bradyarrhythmias; sometimes they may lead to syncope and activation of latent pacemakers with development of different escape rhythms. For instance, AV-block 2nd degree Mobitz I often leads to syncope caused by a short-term asystole (Stokes-Adams attack).



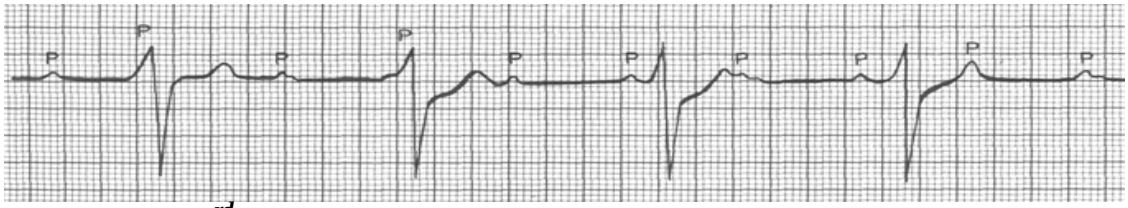
AV-block 1st degree (PQ interval prolongation more than 0,20 sec.)



AV-block 2nd degree Mobitz I (Progressive prolongation of the PQ interval with subsequent loss of QRS complexes)



AV-block 2nd degree Mobitz II (Prolongation of the PQ interval with regularly or irregularly loss of QRS complexes)



AV-block 3rd degree (complete AV-block, asynchronous contraction of atria and ventricles

Figure 2-26. ECG-characteristics of selected heart blocks

Pathophysiological basis for management of arrhythmia. Some arrhythmias may be prognostically benign and do not require treatment. Some arrhythmias may be potentially dangerous and require immediate intervention (pharmacological, non-pharmacological or both). Most antiarrhythmic drugs have a lot of mechanisms of action; however, they may be classified as following:

- Class I drugs block fast inward Na^+ channels with decrease in phase 0 of action potential and delaying intracardiac conduction (quinidine, procainamide, lidocaine, etc.);
- Class II drugs are effective in arrhythmias due to excessive sympathetic stimulation and include β-adrenergic antagonists;
- Class III drugs prolong the duration of the action potential and refractoriness (amiodarone, sotalol, bretilium);
- Class IV drugs include calcium channel antagonists (verapamil, diltiazem).

Asymptomatic heart blocks require no any therapy. Some symptomatic blocks require atropine or β-adrenergic agonists to increase the heart rate or temporally cardiac pacing. Many symptomatic blocks need in permanent (implanted) pacemakers, which now can also terminate episodes of ventricular fibrillation. Radiofrequency catheter ablation is widely used now to eliminate different tachyarrhythmias via irreversible tissue destruction. Surgical accessory conducting pathway ablation is an effective method of treatment patients with Wolff-Parkinson-White syndrome.

3. DISORDERS OF REGULATION OF VASCULAR TONE. ARTERIAL HYPERTENSION. ARTERIAL HYPOTENSION

Blood pressure (BP) is the force exerted by the blood against any unit area on the vessel wall. In the routine clinical practice, systolic and diastolic blood pressure is measured with the auscultatory (Korotkoff) method. Arterial blood pressure is regulated by several interrelated systems. That is why blood pressure is an integral indicator depending on different parameters (Fig. 2-27).

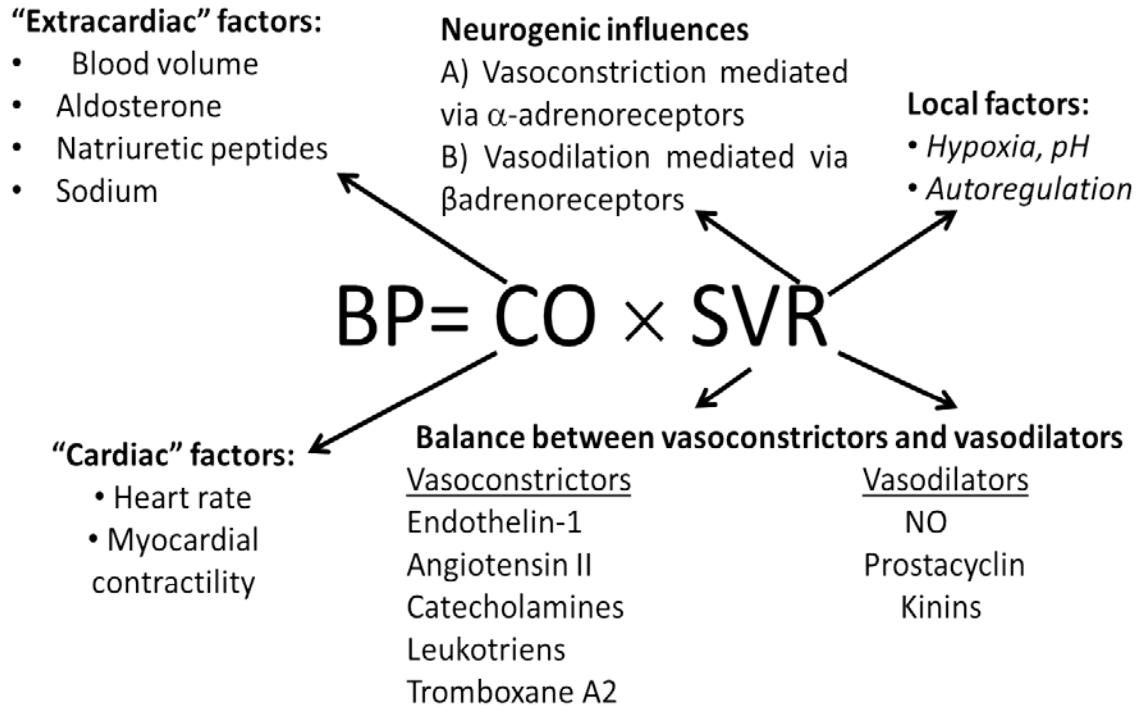


Figure 2-27. Factors determining arterial blood pressure

To better understanding pathogenesis of arterial hypertension or hypotension it is necessary to know mechanisms of blood pressure regulation. These basic controlling mechanisms can be artificially subdivided into (1) rapid, acting within second or minutes; (2) intermediate, acting following several minutes after a shift in the blood pressure, and (3) long-term mechanisms, activating within a few hours after a change in the blood pressure and acting at least during several days.

Rapid BP regulating mechanisms include:

- The baroreceptor feedback mechanism, which is initiated by baroreceptors, or stretch receptors in the walls of large arteries. Stimulation of baroreceptors after sudden elevation of the BP (maximum at about 180 mm Hg) transmits signals to the medulla with subsequent inhibition of the vasoconstrictor center of the medulla and excitation of the vagal center. As a result, vasodilation (both arterial and venous) and bradycardia develop with decrease in the BP.
- The central nervous system ischemic response is activated during brain hypoperfusion and ischemia. This response is resulted from directly stimulation of neurons of vasomotor center by ischemia. Main goal of this response, which is

characterized by a rise of the BP, is to support relatively normal cerebral perfusion.

- The chemoreceptor mechanism, mediated by chemoreceptors. These receptors are located in the carotid bodies and aortic bodies. After sudden fall of the BP, the blood supply of carotid bodies becomes severely reduced with decreased PaO_2 and increased $PaCO_2$ in these structures. Activation of chemoreceptors results in the sending of impulses in the vasomotor center with its excitation and corresponding rise in the BP.

The intermediate BP regulating mechanisms are following:

- Vasoconstriction due to the activation of RAS. When the BP falls, juxtaglomerular cells produce more renin from the prorenin. Renin is an enzyme converting angiotensinogen, produced by the liver, to the angiotensin I. The latter under action of angiotensin converting enzyme (ACE) converts to the angiotensin II, which is a potent vasoconstrictor. This vasoconstrictor system requires near 20 minutes for its powerful activation.
- The stress-relaxation mechanism. After elevation of the BP stretch of blood vessels leads to decrease in their filling with blood and decrease in elevated blood pressure.
- The capillary fluid shift mechanism. When BP falls, interstitial fluid due to osmotic force is absorbed in the capillaries to increase blood volume and to maintain blood pressure. In contrast, after rise in the BP due to Starling's forces fluid escape capillaries thus lowering blood pressure.

The long-term mechanisms involve:

- The renal-blood volume mechanism. For simple, when the BP rises too high, kidneys begin to excrete more urine thus relieving the pressure (so-called pressure diuresis and pressure natriuresis).
- The RAAS activation. Angiotensin II itself can stimulate kidneys to retain sodium and water. It also stimulates aldosterone production by adrenal glands with similar effects (Na^+ retention). This system interacts with many others BP regulating systems. For instance, increased osmolality of the blood stimulates the thirst center and secretion of antidiuretic hormone (ADH) by the hypothalamus. ADH is responsible for increased water reabsorptions by the kidneys. In turn, volume expansion stimulates atrial natriuretic peptide (ANP) secretion by the heart. ANP mediates natriuresis and vasodilation.

Stable impairment of BP maintaining mechanisms may lead to arterial hypertension or hypotension.

Arterial hypertension is a stable elevation of systolic and/or diastolic BP ≥130/80 mm Hg (AHA/ACC, 2017). It was estimated that by the year 2000 about 25% of the adult world population were hypertensive and that this rate will increase to 60% by the year 2025. Arterial hypertension basically can be classified into primary (essential, idiopathic), which takes up to 95%, and the less common (5%) secondary (symptomatic) arterial hypertension. According to BP level, arterial hypertension subdivides into several stages (Table 2-6).

Table 2-6. Classification of arterial hypertension according with BP (AHA/ACC, 2017)

	Systolic BP, mm Hg	Diastolic BP, mm Hg
Normal BP	<120	<80
Prehypertension	120-129	<80
Hypertension, stage 1	130-139	or 80-89
Hypertension, stage 2	140-159	or 90-99
Hypertension, stage 3	≥160	≥100

If patient has normal diastolic, but increased systolic BP, isolated systolic hypertension may be diagnosed. In contrast, patients with normal systolic, but elevated diastolic BP have isolated diastolic hypertension.

Primary (essential) arterial hypertension

Primary (essential) arterial hypertension is a multifactorial disease, which is resulted from the combination of three groups of etiologic factors:

- Genetic predisposition;
- Early developmental programming
- Environmental factors.

Role of the genetic predisposition in the development of primary arterial hypertension. In most cases, this disease is polygenic, whereas some rare, with as a rule, autosomal-recessive type of inheritance, forms of primary arterial hypertension are described (Table 2-7).

Table 2-7. Selected forms of monogenic primary arterial hypertension

Disease	Mutation, type of inheritance	Pathogenesis of arterial hypertension
Glucocorticoid-remediable aldosteronism	Duplication of genes encoding aldosterone synthase and 11β-hydroxylase, dominant	Ectopic expression of protein with aldosterone-synthase like enzymatic activity, Na^+ retention and volume expansion
Liddle's syndrome	Mutations in gene encoding sodium epithelial channel in the kidneys, dominant	Increased activity of epithelial sodium channel results in volume expansion
Apparent mineralocorticoid excess	Mutation in the gene, encoding 11β-hydroxilase, recessive	Reduced inactivation of cortisol, mineralocorticoid-like activity of cortisol, enhanced sensitivity of vSMCs to vasoconstrictors

Polymorphism of at least 50 genes associates with increased risk of arterial hypertension. These affected genes involve those encoding components of RAAS, NO-synthases, enzymes, which catalyze vasoregulators synthesis, receptors for different vasoconstrictors and vasodilators, etc. The list of gene-candidates is growing

now. However, epigenetic regulation of genes, whose products participate in the regulation of BP, is a possible candidate for explanation of stable changes of genes activity under influences of different lifestyle and environmental factors.

Role of the early developmental programming in the pathogenesis of primary arterial hypertension. A growing body of evidence supports the concept that changes in the intrauterine milieu during "sensitive" periods of embryonic development (due to uteroplacental insufficiency, maternal low-protein diet, or maternal overnutrition, vitamin A deficiency, exposure exogenous or endogenous glucocorticoids, ethanol exposure, etc.) or in infant diet or maternal care after birth affect the developing individual, resulting in general health alterations later in life. This phenomenon is referred to as "developmental programming" or "developmental origins of health and disease." The risk of developing late-onset diseases such as arterial hypertension, chronic kidney disease, obesity or type 2 diabetes is increased in infants born prematurely at <37 weeks of gestation or in low birth weight infants weighing <2500 g at birth. At least several mechanisms "program" the development of arterial hypertension in later life after poor early development: (1) oligonephropathy; (2) impairment of natriuresis; (3) hyperactivity of the SNS; (4) hyperactivation of generalized and local RAS; (5) endothelial dysfunction; (6) microcirculatory rarefaction. Oligonephropathy is a decrease number of nephrons in the kidneys. Such oligonephropathy results in the decrease of glomerular filtration area with a subsequent hyperfiltration by residual nephrons with their injury and further loss of nephrons ("vicious circle"). As a result, critical decrease in nephrons number associates with impairment of natriuresis and arterial hypertension in the future life. Stable epigenetic marks (See the Textbook "General pathophysiology: the essentials") may play an important role in the developmental programming of primary arterial hypertension.

Role of environmental factors initiating stable elevation of the BP. Increased morbidity among population of industrialized factors explains links between inadequate lifestyle and expansion of arterial hypertension. These adverse lifestyle factors include low level of the physical activity, smoking, incorrect diet (overeating, great consumption of red meat, fats, carbohydrates, sodium chloride, high alcohol intake, vitamin D deficiency, heavy coffee consumption, etc.), obesity, chronic stress, decreased duration of night sleep. That is why recommendations concerning lifestyle changes may significantly improve natural history of arterial hypertension and patients' quality of life.

Basically, primary arterial hypertension has several mechanisms of development:

- Stable activation of the SNS activation;
- Impairment of natriuresis;
- Stable activation of RAAS;
- Endothelial dysfunction;
- Dysregulation of Na^+ and Ca^{2+} homeostasis in vascular smooth muscle cells;
- Abnormal development of kidneys and/or blood vessels.

The mechanisms of increased sympathetic nervous system activity in hyper-

tension are complex and involve alterations in baroreflex and chemoreflex pathways at both peripheral and central levels. Arterial baroreceptors are reset to a higher pressure in hypertensive patients, and this peripheral resetting reverts to normal when arterial pressure is normalized. This baroreflex resetting seems to be mediated, at least partly, by a central action of angiotensin II, ROS and endothelin-1. Besides impaired baroreceptor and chemoreceptor reflexes, increased SNS activity may be caused by genetic factors, psychological factors, hyperresponsivity to stress, insulin resistance, obesity, dietary salt sensitivity and vascular compression of the medulla. Outcomes of SNS hyperactivation are summarized in the Fig. 2-28. Thus, sympathetic mechanisms contribute to the development of target organ damage, as well as to the pathogenesis of hypertension.

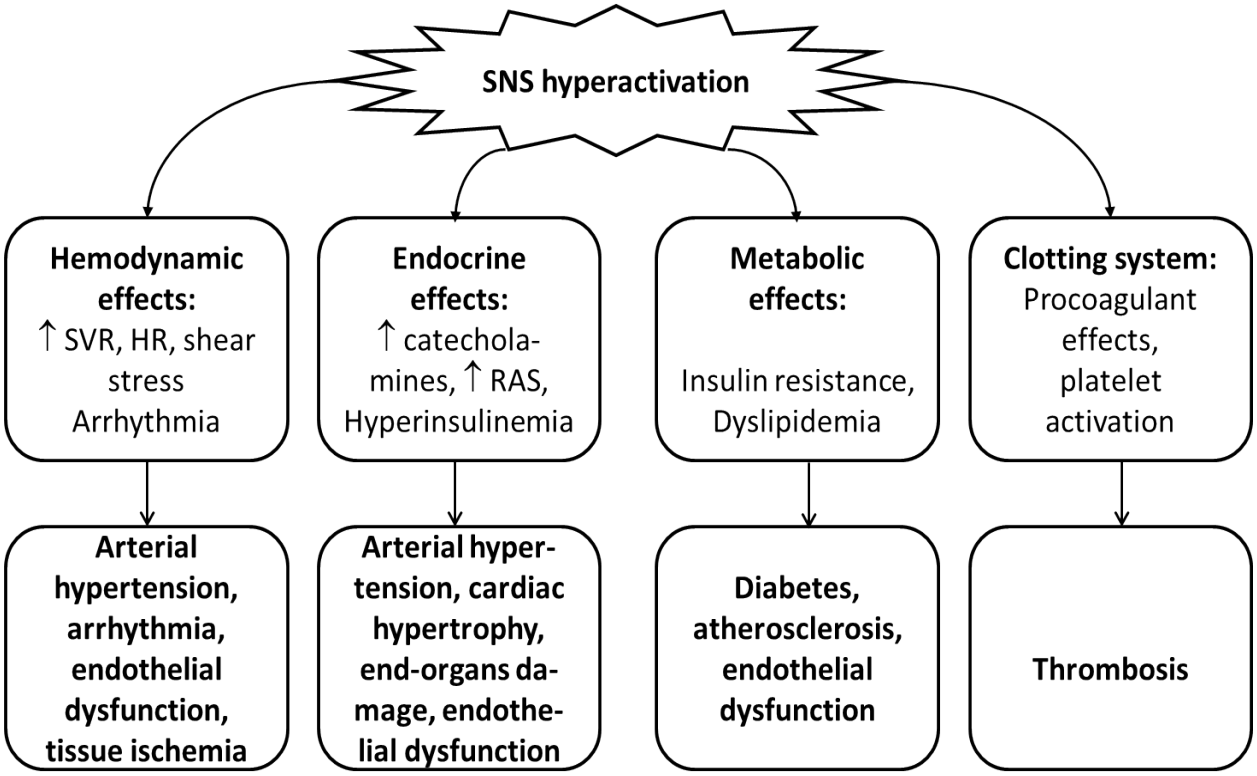


Figure 2-28. Consequences of the stable activation of the SNS

Impairment of natriuresis. In healthy people, as BP rises, the elevation in renal perfusion pressure leads to a decrease in sodium reabsorption in the proximal tubule and, perhaps, in the loop of Henle. As a consequence, body fluid volumes would shrink enough to lower the BP back to its previous level. In patients with primary hypertension a resetting of the pressure-sodium excretion curve prevents the return of BP to normal so that fluid balance is maintained only in the presence of an increased BP. As a consequence of the resetting, when BP is lowered by nondiuretic drugs, reactive sodium retention occurs. Mechanisms of such natriuresis resetting are: (1) stable activation of RAS; (2) an inherited defect in renal function; (3) action of a circulating inhibitor of the Na^+/K^+-ATPase pump (ouabain-like peptides), which increase intracellular sodium and thereby mobilize calcium from intracellular stores with subsequent renal sodium retention, rise of SVR, and, as a result, arterial hypertension.

Activation of the RAAS. Main components of the RAAS, causes and consequences of its activation were discussed in the Part II – Heart failure. Renin is produced by juxtaglomerular cells in the kidneys. It converts angiotensinogen to the angiotensin I. Further, angiotensin converting enzyme (ACE) converts angiotensin I to the angiotensin II. Angiotensin II increases blood pressure by various mechanisms:

(1) Constricting resistance vessels (↑ SVR);
(2) Stimulating aldosterone synthesis and release and renal tubular sodium reabsorption (↑CO);
(3) Stimulating thirst and release of antidiuretic hormone (↑CO);
(4) Enhancing sympathetic outflow from the brain (↑ SVR and ↑ CO).

This knowledge explains reasonability of ACE inhibitors ("-prils") administration to patients with arterial hypertension. It was investigated, that Ang II acts through different subtypes of receptors. Several subtypes of receptors to Ang II were described, but effects mediated by subtypes AT1 and AT2 receptors seem to be most important (Fig. 2-29).

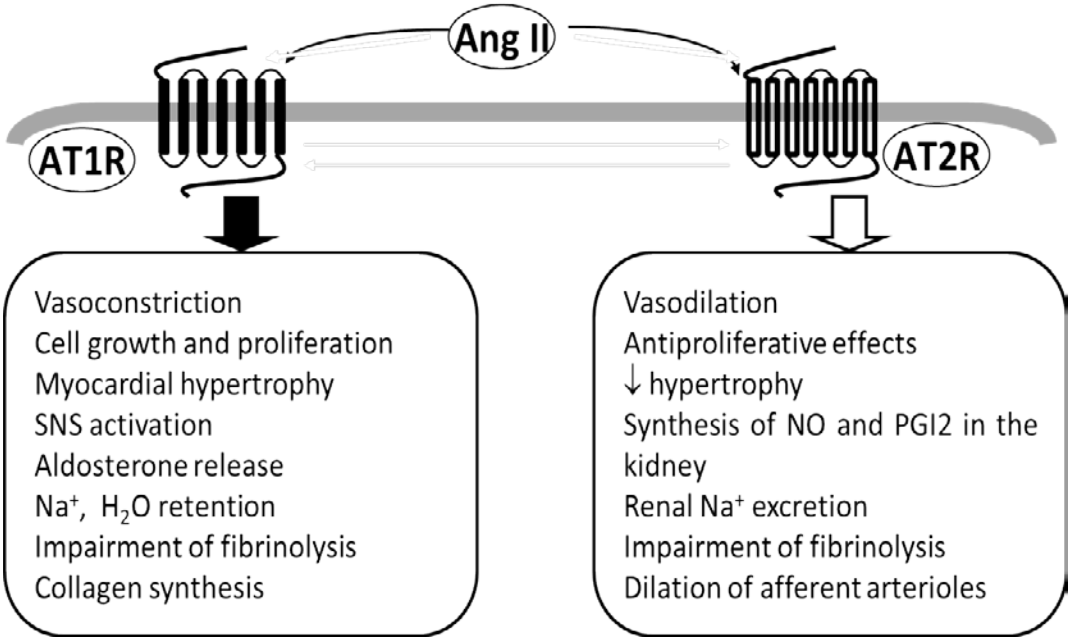


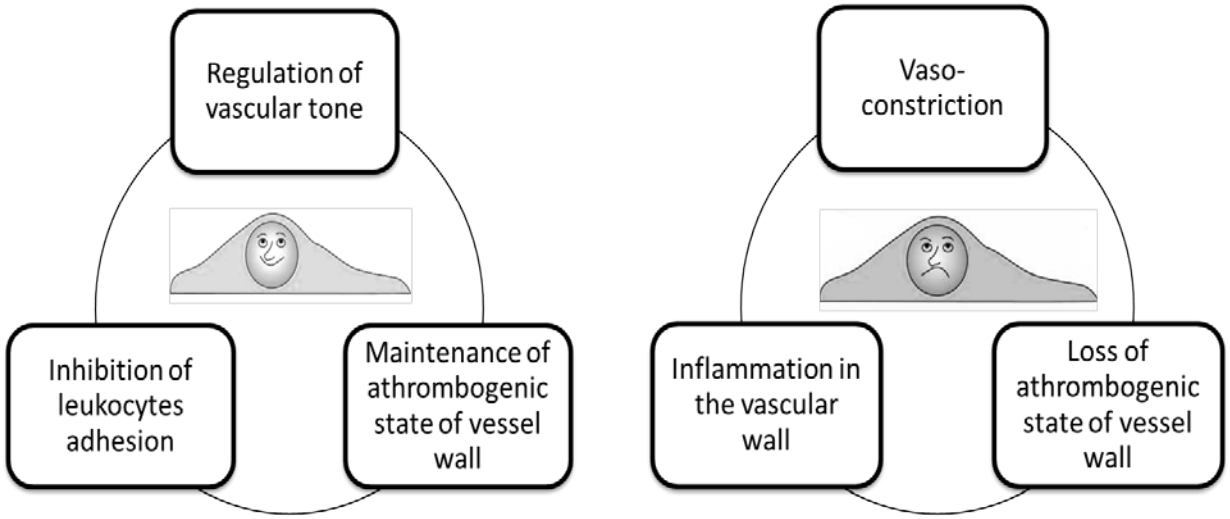
Figure 2-29. Opposite effects of AT1R and AT2R activation

Thus, activation of AT1R has detrimental role in the elevation of the BP and development of complications of arterial hypertension. That is why AT1R blockers ("-sartans") are widely used in the clinical practice.

Endothelial dysfunction is a potentially reversible impairment of endotheliocytes' functions (Fig. 2-30), which is caused by oxidative stress, atherogenic dyslipoproteinemia, hyperglycaemia, components of tobacco smoke, abnormal hemodynamic forces, hypoxia, etc.

In normal conductance arteries, platelets and monocytes circulate freely, and oxidation of low-density lipoprotein is prevented by a preponderance of nitric oxide (NO) formation. At the level of the small arterioles, reduced vascular tone is maintained by constant release of nitric oxide. Endothelin-1 normally induces no

vasoconstriction or only minimal vasoconstriction through stimulation of type A endothelin receptors (ETA) located on smooth-muscle cells and contributes to basal nitric oxide release by stimulating type B endothelin receptors (ETB) on endothelial cells. In the hypertensive microvasculature, decreased activity of nitric oxide and enhanced ETA-mediated vasoconstrictor activity of endothelin-1 result in increased systemic vascular resistance. At the level of conductance arteries, a similar imbalance in the activity of endothelial factors leads to a proatherosclerotic milieu that is conducive to the oxidation of low-density lipoprotein, the adhesion and migration of monocytes, and the formation of foam cells. These activities ultimately lead to the development of atherosclerotic plaques, the rupture of which, in conjunction with enhanced platelet aggregation and impaired fibrinolysis, results in acute intravascular thrombosis, thus explaining the increased risk for cardiovascular events in patients with arterial hypertension.



A) B)

Figure 2-30. Main functions of normal endothelium (A) and clinical outcomes of endothelial dysfunction (B)

However, other than NO gasotransmitters (CO, H_2S) may also play a significant role in the development of arterial hypertension.

Dysregulation of Na^{+} and Ca^{2+} homeostasis in vascular smooth muscle cells. An increased Na^{+}/H^{+} exchanger activity in the vSMCs could play a significant role in the pathogenesis of hypertension, both by stimulating vascular tone and cell growth with increased systemic vascular resistance. Other cotransporters and ion channels disorders may lead to the peripheral vasoconstriction too.

Abnormal development of kidneys and/or blood vessels. Low birth weight, from intrauterine growth retardation, and rapid post-natal weight gain are associated with the subsequent development of hypertension in most surveys due to developmental oligonephropathy (See before) and microvascular rarefaction. The later phenomenon is resulted from decreased microcirculatory vessels per unit of a tissue due to abnormal angiogenesis, or increased dying of cells in microcirculatory vessels' wall, or to impairment of endothelial progenitor cells recruitment and inadequate neoangiogenesis. Microvascular rarefaction leads to the capillary trophic

insufficiency and elevation of the systemic vascular resistance.

Secondary arterial hypertension

It results from renal diseases, endocrine disorders, neurological abnormalities, some cardiac and vascular malformations, and blood diseases.

Renal arterial hypertension

Renal arterial hypertension is classified into renal parenchymal and renal vascular. Different acute and chronic diseases affecting parenchyma of kidneys may complicate by secondary **renal parenchymal arterial hypertension**. These diseases include glomerulonephritis, diabetic nephropathy, tubulointerstitial diseases, and trauma of kidneys. Hemodialysis and kidney transplantation often may coexist with renal arterial hypertension. In contrast, stable elevation of the BP results in the progressive damage of nephrons thus creating a "vicious circle" between damage of renal parenchyma and arterial hypertension. Basic mechanisms of renal parenchymal arterial hypertension are:

- Impaired of renal autoregulation → glomerular hypertension → damage of glomerular cells → inflammation → nephrosclerosis → hyperfiltration → damage of glomerular cells → … ("vicious circle");
- Extravascular volume expansion with increased CO;
- Activation of RAAS;
- Activation of SNS;
- Decreased synthesis of prostaglandins and bradykinin with vasodilating effects;
- Endothelial dysfunction;
- Hyperproduction of parathormone with accumulation of Ca^{2+} in the vSMCs and increased arterial stiffness;
- Release of endogenous digitalis-like factor. Different substances were proposed as this factor. Endogenous digitalis (ouabain)-like factor not only increases SVR directly, but also acts on the CNS with subsequent SNS hyperactivation.

Renovascular hypertension refers to hypertension caused by renal ischemia. Etiology of renovascular hypertension: intrinsic lesions of renal artery, including atherosclerosis, fibromuscular dysplasia, dissection of renal artery, segmental renal infarction, aneurysm of renal artery, emboli, arteritis, large artery vasculitis, arteriovenous malformation or fistula, aortic dissection, thrombosis. Renal ischemia triggers renin release from juxtaglomerular cells in the kidneys with subsequent RAAS activation, increase in SVR and CO (see Fig. 2-27).

Endocrine arterial hypertension

Different disorders of some endocrine glands may lead to secondary arterial hypertension. Diseases of adrenal glands, which may lead to the secondary arterial hypertension, include disorders of adrenal medulla and cortex.

Catecholamine-secreting tumors

Functioning tumors arising outside the adrenal medulla are termed as extra-adrenal **pheochromocytomas**, whereas nonsecreting extra-adrenal tumors are termed **paragangliomas**. Paragangliomas that arise from the specialized chemoreceptor tissue in the carotid body, glomus jugulare, and aortic body have been separately classified as **chemodectomas**, and they may secrete catecholamines. The chromaffin cells synthesize catecholamines from the dietary amino acid tyrosine, which is converted into DOPA and then dopamine. Norepinephrine is the end product, except in the adrenal medulla, where over 75% of the norepinephrine is methylated into epinephrine. Different catecholamine-secreting tumors have different patterns of hormonal secretion. Those that continuously release large amounts of catecholamines may induce sustained hypertension with few paroxysms, since the adrenergic receptors become desensitized after prolonged exposure to their agonists. Tumors that are less active but cyclically release their catecholamine stores may induce striking paroxysms of hypertension with the classic symptoms of a pheochromocytoma, since the receptors are more responsive. Most patients have headache, sweating, and palpitations; many have all three occurring in paroxysms. Some are asymptomatic, and others have their symptoms attributed to concomitant conditions. Most patients have sustained hypertension with superimposed paroxysms. The paroxysm can be brought on in multiple ways, including exercise, bending over, urination, defecation, an enema, induction of anesthesia, smoking, dipping snuff, palpation of the abdomen, or pressure from an enlarging uterus during pregnancy. Pathogenesis of arterial hypertension is following:

1. Catecholamine-induced tachycardia with elevated CO;
2. Increase of SVR after a peak of catecholamine secretion.

Nonselective α-adrenoreceptor antagonists are primarily used for the management of arterial hypertension in patients with pheochromocytoma.

When BP rises above 250/150 mm Hg, it may lead to myocardial ischemia, acute heart failure and arrhythmias. Rarely, the presentation may be as an acute abdomen from spontaneous rupture of the tumor, sudden death after minor abdominal trauma, lactic acidosis, or high fever and encephalopathy. Patients with tumors secreting predominantly epinephrine may rarely present with cardiogenic shock, presumably from decreased cardiac contractibility; from downregulation of β1-receptors in the heart after prolonged exposure to high epinephrine levels and from hypocalcemia of uncertain origin. Prolonged hypotension may also occur by spontaneous necrosis of the tumor or after administration of an β-blocker.

Cortisol excess

Excessive production of cortisol by adrenal cortex also may lead to the secondary arterial hypertension. **Cushing's syndrome** is caused by excess endogenous cortisol with the idiopathic form or excess exogenous steroids in the iatrogenic form. **Cushing's disease** is due to overproduction of ACTH from a pituitary microadenoma with resultant adrenal hyperplasia. Ectopic ACTH production may come from multiple types of tumors. Multiple mechanisms may be responsible for the hypertension in cortisol hypersecretion:

1. High levels of cortisol have mineralocorticoid activity, thus leading to the

blood volume expansion and rise in CO. Moreover, sometimes cortisol hyperproduction coexists with aldosterone hyperproduction.
2. Endothelial dysfunction with lack of vasodepressor mechanisms, including NO, bradykinin and prostaglandins deficiency, and elevation of endothelin-1 level.
3. Increased levels of renin substrate with subsequent RAAS activation.
4. Activation of the SNS.
5. Increased sensitivity of vSMCs to different vasoconstrictors.
6. Obesity, insulin resistance and sleep apnea (See later).

Aldosterone excess

Primary aldosteronism (Conn's syndrome) is the syndrome resulting from the autonomous hypersecretion of aldosterone in the adrenal zona glomerulosa, usually by a solitary adenoma or by bilateral hyperplasia. The classic clinical features of primary aldosteronism are hypertension, hypokalemia, excessive urinary potassium excretion, hypernatremia, and metabolic alkalosis. The pressor actions of aldosterone are generally related to its effects on sodium retention via its action on renal mineralocorticoid receptors with volume expansion. However, aldosterone may increase vascular stiffness with increased SVR. When the extracellular fluid expansion reaches a certain point, Na^+ excretion resumes despite the continued action of aldosterone on the renal tubule. This “escape” phenomenon is probably due to increased secretion of atrial natriuretic peptide. That is why affected patients are not edematous. In case of hyperaldosteronism, activity of juxtaglomerular cells is suppressed, and concentration of renin in the serum falls.

Secondary aldosteronism is resulted from primary hypersecretion of renin by juxtaglomerular cells. Causes of secondary hyperaldosteronism include: renal ischemia of different origin, depletion of intravascular blood volume, sodium-wasting disorders, and hyperplasia of juxtaglomerular cells or tumor originating from these cells, oral contraceptives use. Mechanism of arterial hypertension is similar to those described above.

Arterial hypertension associated with oral contraceptives use

Females receiving oral contraceptives may develop arterial hypertension because of: (1) these drugs cause endothelial dysfunction; (2) they activate juxtaglomerular cells thus stimulating RAAS activity; (3) they impair sensitivity to insulin and lead to insulin resistance. Cessation of oral contraceptives usually results in the normalization of BP.

Disorders of thyroid gland associated with arterial hypertension

Both hyperthyroidism and hyperthyroidism may complicate with secondary arterial hypertension. During hyperthyroidism, it is explained by tachycardia and elevated cardiac output, despite reduced SVR. Patients often have elevated systolic, but normal diastolic BP. In patients with hypothyroidism, hypertension is particularly diastolic. Despite the fact that hypothyroid patients tend to have a low

cardiac output with a decrease in contractility and impaired diastolic relaxation, SVR increases to maintain tissue perfusion. Also hypothyroidism associates with increased activity of SNS.

Growth hormone hyperproduction

Growth hormone hyperproduction in adults is most common resulted from GH-secreting pituitary adenoma with clinical signs of acromegaly. The hypertension in patients with acromegaly is related to: (1) sodium retention and blood volume expansion; (2) increased sympathetic-mediated vasoconstriction; (3) endothelial dysfunction with increased SVR; (4) IGF-1-mediated hypertrophic remodeling of resistance arteries with elevated SVR; (5) sleep apnea.

Hemodynamic causes of secondary arterial hypertension. Coarctation of the aorta

Constriction of the lumen of the aorta may occur anywhere along its length but is seen most commonly in its proximal parts. Clinically coarctation of the aorta is characterized by a hypertension in the upper extremities with diminished or absent femoral pulses. Mechanisms of such hypertension are following: (1) decreased vascular compliance in the proximal aorta; (2) activation of RAAS due to hypoperfusion of kidneys.

Neurologic disorders

Intracranial tumors, especially those arising in the posterior fossa, or abscesses may cause hypertension. Mostly these disorders lead to the hyperactivation of the SNS. Some anxiety-related disorders, for instance, hyperventilation syndrome may lead to arterial hypertension in affected individuals. Mechanisms are illustrated with simple sequences: (1) hyperventilation → metabolic alkalosis → ↑ concentration of intracellular Ca^{2+} in the vSMCs → ↑ SVR; (2) hyperventilation → activation of SNS → tachycardia and peripheral vasoconstriction → ↑ CO and SVR. Arterial hypertension may appear during various acute physical stresses, usually reflecting an intense sympathetic discharge and sometimes activation of RAAS as well as insulin resistance.

Other causes of secondary arterial hypertension

Primary polycythemia (polycythemia vera) is a chronic myeloproliferative disorder. Patients with primary polycythemia are often hypertensive. Firstly, polycythemic hypervolemia in such individuals results in the increase of cardiac output. Secondly, hyperviscosity of the blood leads to the increase of systemic vascular resistance. Thirdly, impaired transcapillary gases exchange in the renal capillaries due to increased blood viscosity may lead to renal hypoxia and activation of RAAS. Similar to hyperviscosity mechanism of secondary hypertension was demonstrated in patients with chronic renal failure after **erythropoietin therapy**.

Some **chemical substances and drugs** also may lead to symptomatic hypertension. For example, caffeine is acts as a sympathomimetic, and acutely raises BP by increasing SVR and by an increase in aortic stiffness. Other sympathomimetics

involve cocaine, ephedrine, methamphetamine, nicotine; phencyclidine and phenylpropanolamine. Nonsteroidal anti-inflammatory drugs (NSAIDs) are well known to blunt the antihypertensive effect of most antihypertensive agents. They inhibit prostaglandin-dependent counter-regulatory mechanisms in the kidney. Some selective COX-2 inhibitors strongly elevate risk of cardiovascular catastrophes. Alcohol in excess amounts raises BP; in moderate amounts it may be protective against the development of hypertension. Some drugs (licorice, cortisone, anabolic steroids) have mineralocorticoid (aldosterone-like effects). Many other drugs may cause elevation of BP as an adverse reaction.

Potentially correctable lifestyle factors and arterial hypertension

Obesity, especially abdominal, often associates with arterial hypertension. Mechanisms of such links are indicated on the Fig. 2-31.

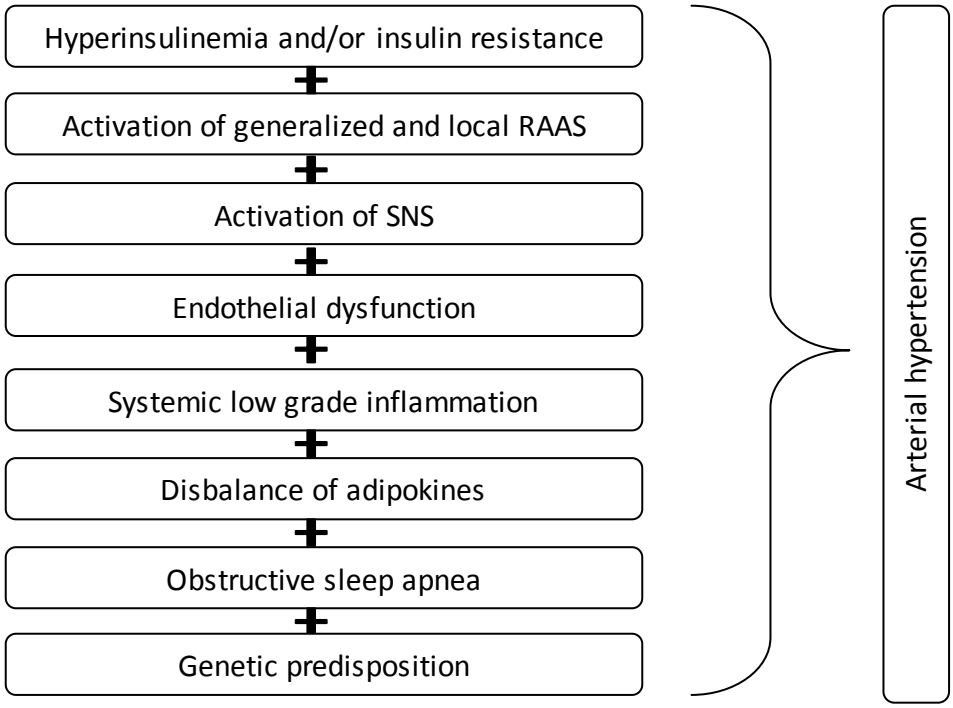


Figure 2-31. Pathogenesis of obesity-related arterial hypertension

Obstructive sleep apnea/hypopnea syndrome characterized by episodes of upper airway obstruction during sleep result in recurrent arousals associated with excessive daytime sleepiness. **The syndrome** is manifested by a complete or partial collapse of the upper airway with persistent effort to breath. Sleep apnea syndrome associates with a number of cardiovascular abnormalities, including arterial hypertension, cardiac arrhythmias, LV systolic or diastolic dysfunction, pulmonary hypertension, RV failure, congestive heart failure, stroke, and accelerated development of the coronary heart disease. That is why sleep apnea syndrome is now considered as a component of metabolic syndrome (See Part IX in the Textbook "General pathophysiology"). Pathogenesis of secondary arterial hypertension associated with sleep apnea is presented in the Fig. 2-32.

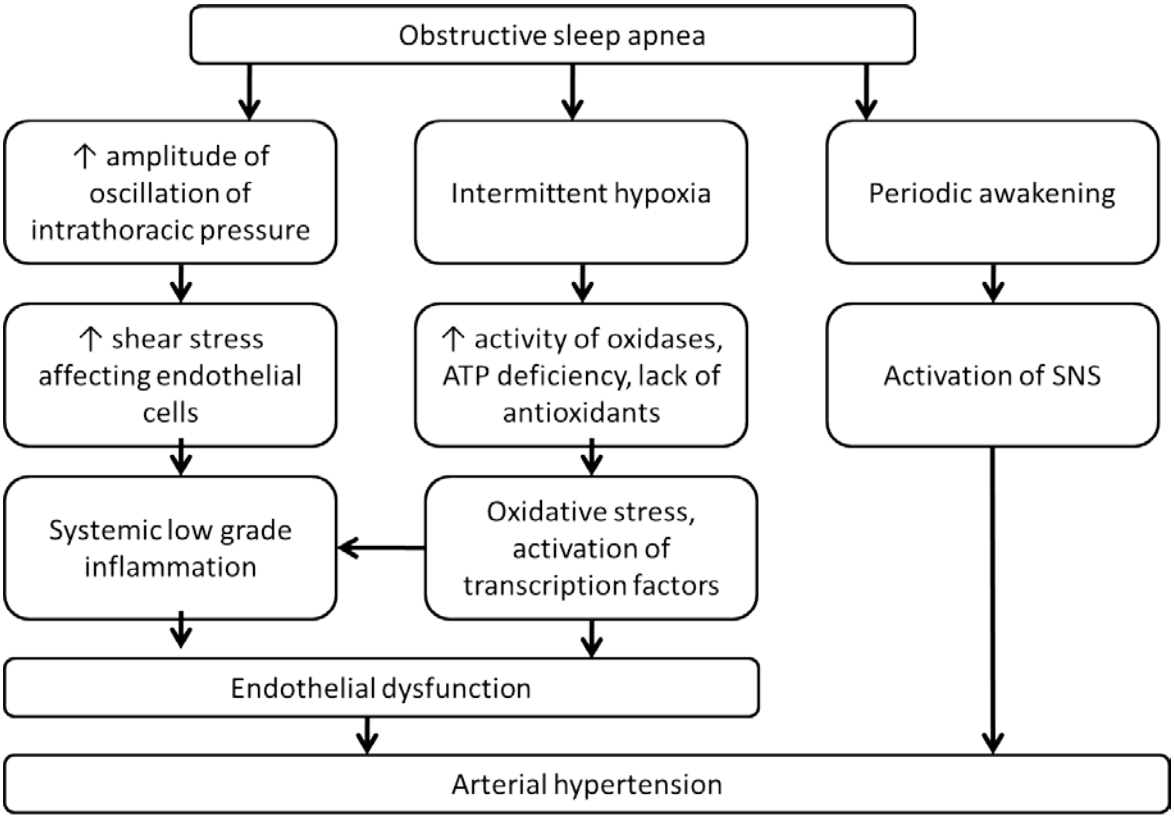


Figure 2-32. Pathogenesis of arterial hypertension in patients with obstructive sleep apnea

However, other non-cardiovascular effects of obstructive sleep apnea, such as excessive daytime sleepiness, increased risk of automobile crashes, cognitive abnormalities, affective disorders and gastroesophageal reflux may significantly impair quality of life.

Insulin resistance is detected commonly in obese individuals. Insulin resistance also may elevate BP via following main mechanisms, which increase both CO and SVR:

- Hyperinsulinemia produces renal sodium retention (at least acutely) and increases sympathetic activity;
- Vascular smooth-muscle hypertrophy develops secondary to the mitogenic action of insulin;
- Insulin modifies ion transport across the cell membrane, thereby potentially increasing the cytosolic calcium levels of insulin-sensitive vascular or renal tissues.

Smoking also links with arterial hypertension via endothelial dysfunction and nicotine-induced release of norepinephrine from adrenergic nerve endings. **Alcohol** doses and risk of arterial hypertension are better described as a U-shape diagram, which meaning that both too low and too high doses similarly result in cardiovascular morbidity. Alcohol abuse leads to the elevation of BP due to sympathetic nervous hyperactivity, vascular cell membrane defects with accumulation of calcium inside vSMCs, RAAS activation and endothelial dysfunction. **Sedentary lifestyle** associates with endothelial dysfunction and activated SNS with resultant

arterial hypertension. **"Western" diet** rich in the sodium chloride, red meat, saturated fats and carbohydrates may predispose to arterial hypertension. This type of nutrition results in endothelial dysfunction and systemic low grade inflammation. Links between overconsumption of NaCl and arterial hypertension is illustrated in the Fig. 2-33.

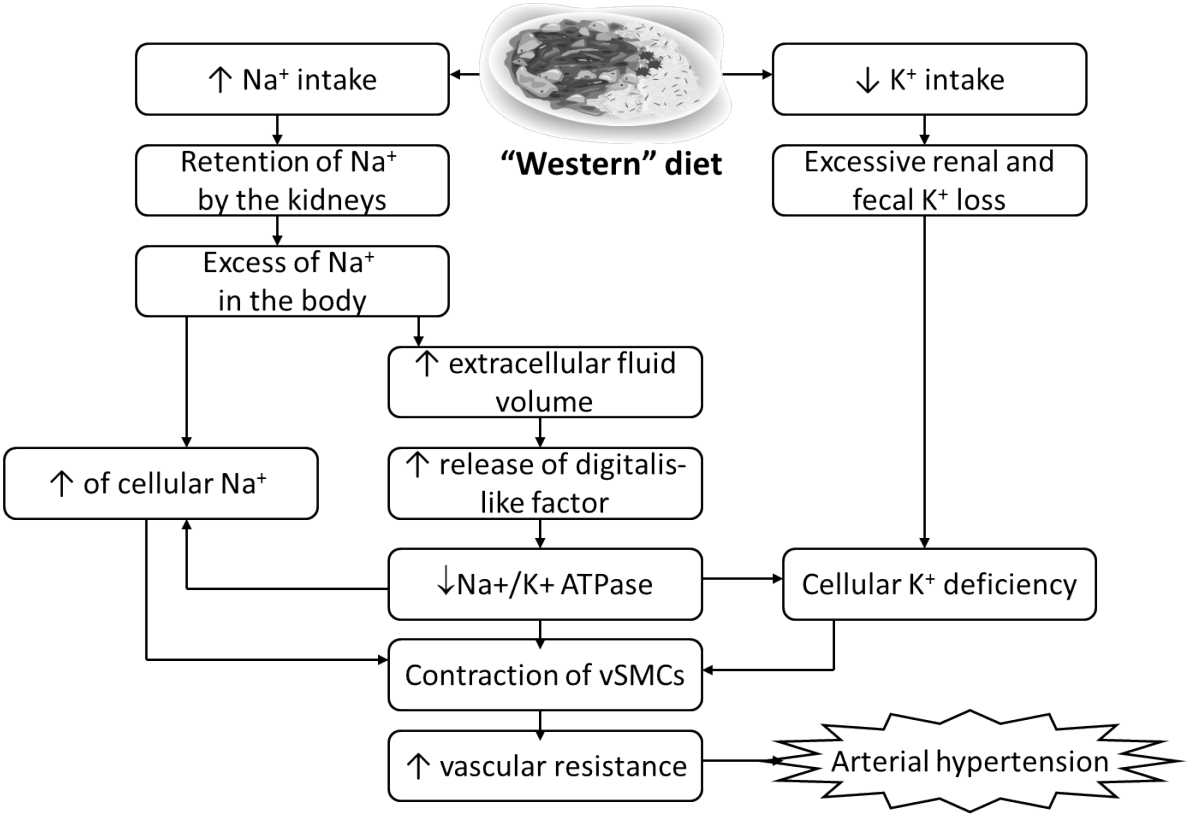


Figure 2-33. High intake of the sodium chloride and arterial hypertension

Hypertensive emergency and urgency

Hypertensive emergency is a situation that requires immediate reduction in blood pressure with parenteral agents because of acute or progressing target organ damage. Systolic BP during hypertensive emergency is ≥ 180 mm Hg, diastolic BP ≥ 110 mm Hg. Target organ damage includes eyes (retinal hemorrhage or an exudate), brain (symptoms of increased intracranial pressure, subarachnoid or cerebral hemorrhage), heart (left ventricular dysfunction, acute pulmonary edema, angina pectoris, arrhythmias), kidneys (with development of hematuria, proteinuria, and acute renal failure), blood vessels (rupture, aortic dissection). Hypertensive urgency is a situation with markedly elevated BP but without severe symptoms or progressive target organ damage, wherein the BP should be reduced within hours, often with oral agents.

Etiology of such hypertensive crisis: discontinuation of therapy; autonomic hyperactivity, collagen-vascular diseases, some drugs, glomerulonephritis, head trauma, neoplasms, preeclampsia and eclampsia during pregnancy, and renovascular hypertension. Several mechanisms were proposed for explanation of pathogenesis of hypertensive emergency. Most popular explanations are sudden rise in SVR and impairment of cerebral autoregulation. First is due to releasing of a number of

vasoconstrictors (See Table 6-1 in the Textbook "General pathophysiology: the essentials") with subsequent rise in SVR and ischemia of peripheral organs. Cerebral autoregulation is the ability of the blood vessels in the brain to maintain a constant blood flow in the certain range of the perfusion pressure (in normotensives in the range of 60-120 mm Hg). Patients with chronic and irregularly treated hypertension can tolerate higher arterial pressure due to the shift of the autoregulation curve to the right. This means that brain perfusion becomes better in higher range of perfusion pressure, for example, 110-160 mm Hg. Moreover, ability of brain arteries to the autoregulation (constriction or dilation in response to rise or fall of the perfusion pressure, accordingly) may impair. That is why in patients with arterial hypertension sudden or rapid rises in blood pressure may cause hyperperfusion and increased cerebral blood flow, causing increased intracranial pressure and cerebral edema with clinical signs of acute hypertensive encephalopathy. In patients with chronic hypertension autoregulation of renal arteries also impair. During a hypertensive crisis, this can lead to acute renal ischemia with more pronounced RAAS and SNS activation, thus creating a "vicious circle" and severe arterial hypertension. Microvascular changes may play a significant role in the pathogenesis of hypertensive crisis. Endothelial injury can occur as a consequence of severe elevations in BP, with subsequent fibrinoid necrosis of the arterioles following microvascular thrombosis, microvascular hemolysis, more severe vasoconstriction, ischemia and subsequent rise in SVR with formation of a "vicious circle".

Therapy of hypertensive emergency requires the administration of an intravenous sodium nitroprusside injection. In less urgent cases, oral agents (See below) can be used. It is necessary to point that BP should be lowered gradually, no more than 25% (within minutes to 1 or 2 hours), and then toward a level of 160/100 mm Hg within a total of 2–6 hours. Abrupt fall of BP can precipitate coronary, cerebral, or renal ischemia and, possibly, infarction.

Complications of arterial hypertension

Arterial hypertension is thought as a "silent killer" now, because it leads to chronically developed, but potentially fatal complications including vascular changes, myocardial hypertrophy with development of the heart failure, damage of kidneys, and accelerated atherogenesis progressing to the coronary (ischemic) heart disease.

Vascular changes. In response to hemodynamic load due to pressure and/or volume overload, local action of angiotensin II and aldosterone, ROS and RNS, cytokines, growth factors, vascular remodeling becomes to be activated. Remodeling is a structural change of the medial layer in the vascular wall during hypertension. It is a result of changes in both cellular and acellular compartments. Basic mechanisms of vascular remodeling during hypertension are:

- vSMCs growth and migration;
- Endothelial dysfunction;
- Low-grade inflammation in the vascular wall
- Increased synthesis of components of extracellular matrix;

- Excessive degradation of extracellular matrix;
- Apoptosis of vascular cells.

As a result, small arteries may undergo hypertrophic or eutrophic remodeling (Fig. 2-34). Hypertrophic remodeling means increase of cross-sectional area, eutrophic – no change in cross-sectional area. These forms can be inward (with reduction in the lumen diameter) or outward (with increase in lumen diameter). Hypertrophic inward remodeling, especially after functional vasoconstriction, creates most increase in the SVR provoking further rise in the BP and explains impairment of arterial blood supply in such patients.

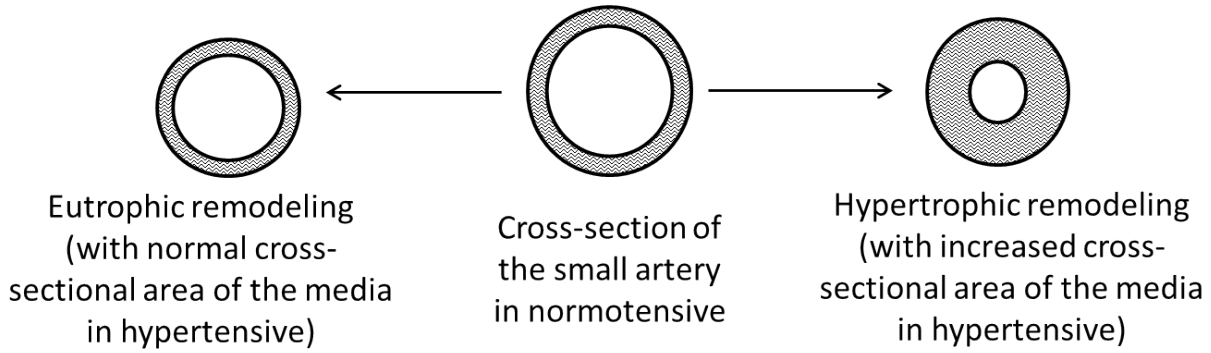


Figure 2-34. Different types of vascular remodeling in arterial hypertension

Progression of arterial hypertension also causes arterial stiffness (reduced their elasticity). The stiffness of large elastic arteries increases significantly after the 55 years of age. Arteriosclerosis in large conduit arteries results from collagen deposition and smooth-muscle cell hypertrophy, as well as thinning, fragmenting, and fracture of elastin fibers in the media. In addition to these structural abnormalities, endothelial dysfunction, systemic low grade inflammation, paracrine acting substances (angiotensin II, aldosterone, ROS, RNS and endothelin-1), and advanced glycated end products (AGEs) may play a significant role. Arterial stiffness depends on the three basic parameters: arterial wall stiffness, wall thickness and lumen diameter. Different indexes including pulse-wave velocity were proposed to assess arterial stiffness. Clinical consequences of arterial stiffness are illustrated in the Fig. 2-35. Arterial stiffness positively associates with cardiovascular morbidity and mortality. Arterial stiffness in aging persons leads to isolated systolic arterial hypertension.

Other vascular complications of arterial hypertension include accelerated atherosclerosis and microvascular disorders. The first explains why arterial hypertension doubles risk of symptomatic ischemic heart disease. Atherosclerosis combined with high pulsatile wave stress play an important role of the pathogenesis of aortic dissection, mainly in the descending aorta. Aortic aneurysm also may be detected in patients with arterial hypertension. Hypertension is also the major cause of stroke, ischemic or hemorrhagic. Gradual development of atherosclerotic plaques in cerebral arteries leads to the chronic brain hypoperfusion, cognitive disorders and dementia.

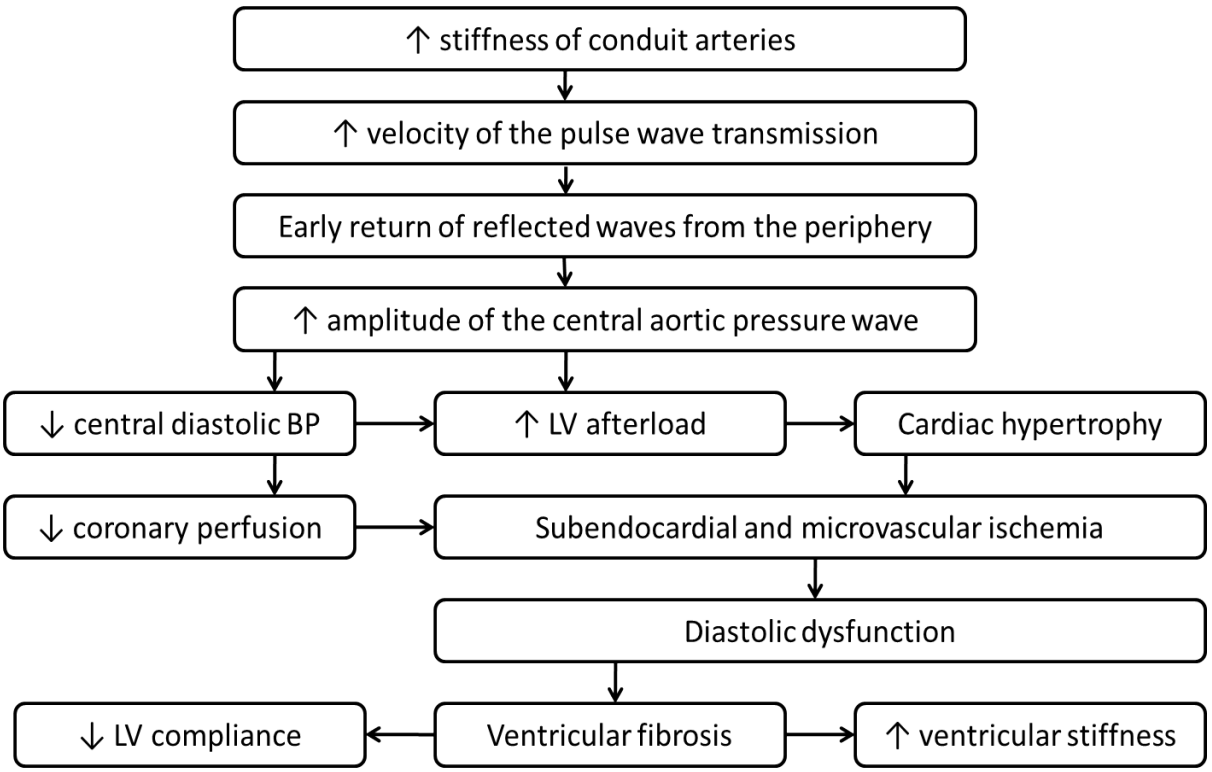


Figure 2-35. Clinical outcomes of arterial stiffness

Microvascular abnormalities lead to the microvascular rarefaction. It is pathological process which is characterized by an abnormally low spatial density of microvessels in the organs and tissues. Three types of microvascular rarefaction may be present in arterial hypertension: (1) functional (due to peripheral vasoconstriction); (2) structural (caused by hyalinosis and sclerosis of arterioles) and (3) combined. Microvascular rarefaction also may be caused as an abnormal intrauterine development as an impaired neoangiogenesis. The latter is resulted from decreased amount of endothelial progenitor cells due to their apoptosis or their poor response on the stimulation by growth factors. Microvascular rarefaction has two basic clinical outcomes: increase in SVR and capillary-trophic insufficiency thus leading to the hypertensive end-organ damage. One of the most detected microvascular disorders is hypertensive retinopathy which is characterized by narrowed arterioles) and, in more severe cases, retinal hemorrhages and exudates along with swelling of the optic nerve head (papilledema). These changes are seen on funduscopic examination.

Myocardial hypertrophy and cardiac remodeling is an adaptive (but "expensive") response of the heart to its volume and/or pressure overload. To recall your knowledge about causes, mechanisms and outcomes of myocardial hypertrophy and remodeling it is strongly recommended to revise material explained in the Part "Heart Failure" in the present Textbook. Myocardial hypertrophy and remodeling lead to diastolic and/or systolic dysfunction, provoke ischemic episodes and arrhythmia, and may lead to congestive heart failure.

Renal damage. Hypertension-associated renal damage manifests as proteinuria (initially as microalbuminuria), reduced glomerular filtration rate, or pro-

gression to end-stage renal disease. The most likely cause of these pathologies is loss of renal autoregulation which normally attenuates the transmission of increased systemic pressure to the glomeruli, and impair of glomerular filter leading to glomerular hypertension, glomerulosclerosis, progressive renal dysfunction and protein leakage in the interstitium. Hypertensive nephrosclerosis morphologically is seen as arteriolar sclerosis and hyalinosis, global and focal glomerular sclerosis, interstitial fibrosis with tubular atrophy, and chronic interstitial inflammation. Renal damage creates "vicious circle" between arterial hypertension and augmentation of kidneys involvement in the pathological process.

Pathophysiological basis for the treatment of arterial hypertension

Arterial hypertension is chronic disease that is why main goals of its treatment are stabilization of the blood pressure and retarding of hypertensive end-organ damage. Whereas arterial hypertension is a multifactorial disease, treatment approaches should include lifestyle modification, pharmacotherapy and invasive procedures in some cases. Bilateral destruction of the renal sympathetic nerves by radiofrequency ablation catheters is widely used now with reduction of BP more than one year after treatment. Secondary arterial hypertension requires correct management of underlying disorder.

Lifestyle modification requires: adequate physical activity, correct work-rest regime, correct diet (with NaCl consumption no more than 6 g per day, rich in fruits, vegetables, sea food), weight reduction, moderation of alcohol consumption, and withdrawal of smoking.

Pharmacotherapy of arterial hypertension involves several groups of drugs:

- Diuretics, which decrease BP initially by reducing reabsorption of Na^+ in the renal distal convoluted tubules and later by decreasing SVR;
- Adrenergic-inhibiting drugs including different β-adrenoblockers acting on the CO and/or SVR;
- Direct vasodilators, which are especially useful for the management of hypertensive emergency;
- Calcium channel blockers with vasodilating effects;
- Angiotensin-converting enzyme inhibitors, which block generalized and local RAAS thus having hypotensive activity and ability to delay end-organ damage progression;
- Angiotensin II receptors blockers;
- Mineralocorticoid antagonists;
- New drugs (direct renin inhibitors, vasopeptidase inhibitors).

Arterial hypotension

Arterial hypotension is a decrease in the BP lower than 100/60 mm Hg in males and lowers than 95/60 mm Hg in females. Arterial hypotension may be physiological (in some normal healthy individuals, athletes or as an adaptive reaction in highland, the tropics or beyond the Arctic Circle) or pathological. The latter may be acute and chronic. Acute arterial hypertension often results from:

- Acute cardiovascular insufficiency due to sudden suppression of the myocardial contractility, abrupt severe vasodilation and/or acute hypovolemia;
- Shock of any etiology;
- Overdose of antihypertensive drugs.

Causes of chronic arterial hypotension are summarized in the Fig. 2-36.

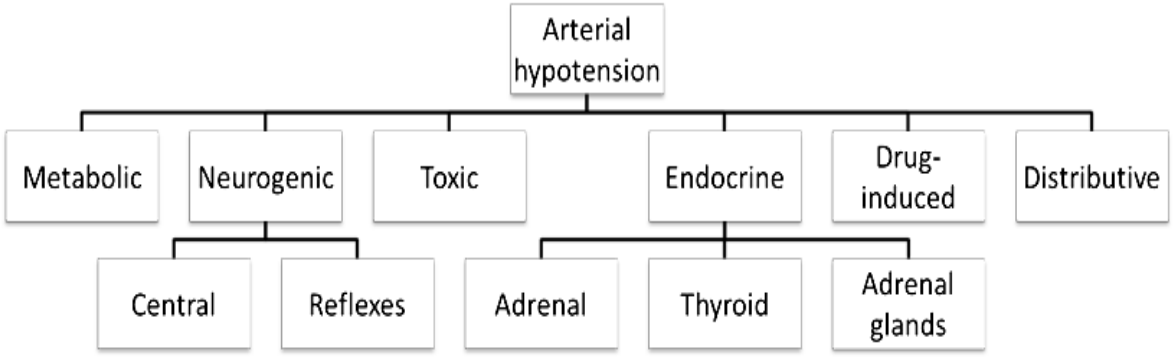


Figure 2-36. Etiologic-based classification of the chronic arterial hypotension

Neurogenic arterial hypotension may result from so-called "central" and "peripheral" causes. Pathogenesis of the "central" arterial hypotension is proposed in the Fig. 2-37. This type of hypotension is due to functional alterations in the vegetative nervous system or morphological damage of those brain structures which regulate BP. Such morphological damages include cerebral trauma (brain concussion or brain contusion), disorders of cerebral blood flow (ischemia or pasive hyperemia), degenerative diseases, disorders of catecholamine release during extreme physical exercises, orthostatic syncope and Shy-Drager syndrome. The latter were described in the Textbook "General pathophysiology: the essentials". Basically two mechanisms explain pathogenesis of these disorders:

1. Decrease activity of the SNS and loss its prevailing influence on the cardiovascular system;
2. Absolute or relative predomination of the parasympathetic nervous system's tone.

   Peripheral causes of the chronic arterial hypotension are, in fact, different reflexes. Such type of arterial hypotension is common in neurosyphilis, lateral amyotrophic sclerosis, syringomyelia and peripheral neuropathies (complicated diabetes mellitus, infections, intoxications) and is characterized by an impairment of impulses transmission from the vasomotor center to the heart and blood vessels. Loss of tonic effects of the SNS results in decrease in heart rate, SVR, myocardial contractility and, as a result – to the arterial hypotension.

   Endocrine arterial hypotension is a complication of a certain endocrine diseases with hypofunction of endocrine glands (See Fig. 2-36). Universal mechanisms of endocrine arterial hypotension are reviewed in the Fig. 2-38.

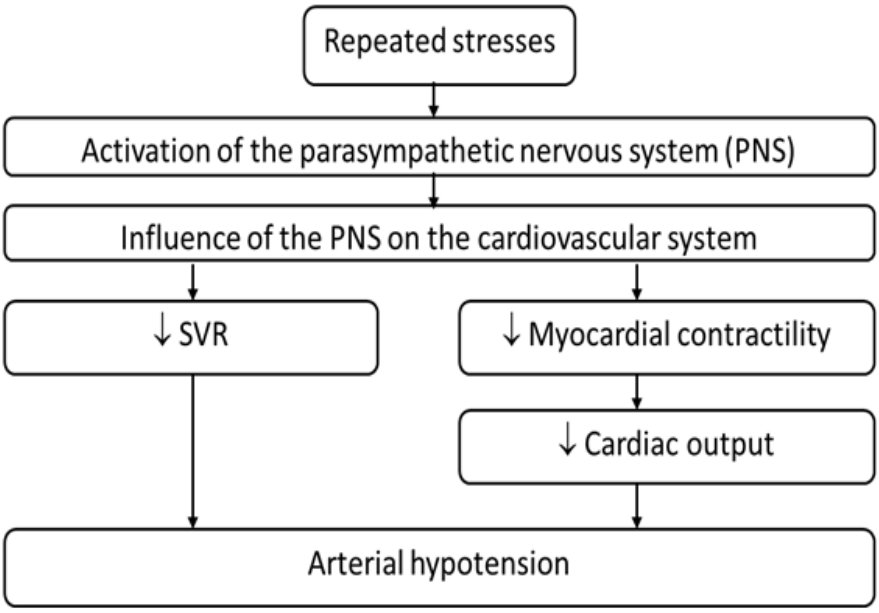


Figure 2-37. Simplified mechanism of the central chronic arterial hypotension

Arterial hypotension of adrenal origin is resulted from hypofunction of adrenal medulla or adrenal cortex. Most common cause of adrenal medulla failure is an adrenal apoplexy (Waterhouse-Friderichsen syndrome), which commonly complicates meningococcal sepsis. This syndrome manifests clinically by an acute cardiovascular failure with uncontrolled arterial hypotension and depression of myocardial contractility caused by catecholamines deficiency. Insufficiency of adrenal cortex may be primary (Addison's disease) caused by cortex destruction following trauma, tuberculosis, adrenal neoplasms with cortex destruction, autoimmune-mediated cortex damage or as a result of congenital hypoplasia, or secondary (due to pituitary ACTH hyposecretion), or tertiary (due to deficiency of hypothalamic ACTH-releasing hormone). Such causes lead to decrease in SVR and CO with resultant arterial hypotension.

Hypopituitarism per se also may result in the arterial hypotension. It may be inborn or acquired; total or partial. Acquired total hypopituitarism includes postpartum hypopituitarism (Sheehan's syndrome, caused by ischemic necrosis of the pituitary gland after severe postpartum hemorrhage) and Simmonds's disease (necrosis of the pituitary gland after a craniocerebral trauma, severe acute hemorrhage, primary and metastatic tumors, and exposure of ionizing irradiation). Depending on the severity and localization of necrosis in the pituitary gland, hypofunction of adrenal gland results in deficiency in all or some from the following hormones: vasopressin, ACTH, TSH, and GH. As a result, SVR and/or CO fall with development of arterial hypotension.

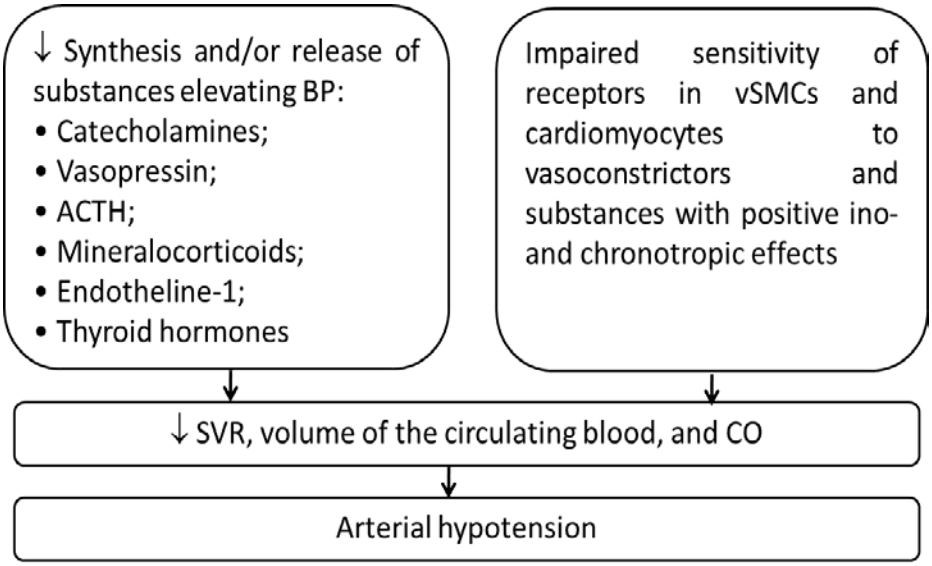


Figure 2-38. General pathogenesis of endocrine arterial hypotension

Hypofunction of the thyroid gland (hypothyroidism) is a common cause of arterial hypotension. Hypothyroidism may be primary (after total or partial thyroidectomy, caused by ionizing irradiation exposure, treatment with radioactive iodine, inflammatory and autoimmune diseases of the thyroid gland – thyroiditis, endemic goiter, tumors of the thyroid gland), secondary (following decreased production of TSH in the anterior pituitary), or tertiary (due to hypoproduction of TSH-releasing hormone by the hypothalamus. Deficiencies of T_3 and T_4 results in the bradycardia and decrease in CO, because of thyroid hormones have positive chronotropic effects and stimulate activity of SNS. Moreover, hypothyroidism often associates with dystrophic changes in the vascular wall and decrease in SVR. However, sometimes hypothyroidism leads to the arterial hypertension (See before).

Metabolic arterial hypotension is rare. Its etiology is: chronic intoxications, infections, food starvation, or severe dehydration. Intoxications, infections or starvation are characterized by an abnormal synthesis or action of vasoconstrictors (endothelin-1, PG F, TX A_2, Ang II, etc.), relaxation of vSMCs, and impaired myocardial contractility. Severe dehydration leads to decrease in CO.

Distributive arterial hypotension may manifest as a postprandial or orthostatic. Postprandial hypotension is seen in some aging or elderly persons after meal due to redistribution of the blood to splanchnic blood vessels. Such postprandial hypotension sometimes provokes myocardial ischemia or ischemic stroke. Pathogenesis of the orthostatic hypotension was described in the Textbook “General pathophysiology: the essentials”.

Unexplained weaknesses, fatigue, disorders of memory, lack of attention are main clinical hallmarks of chronic arterial hypotension. Chronic arterial hypotension impairs quality of the life. It is well known that the range of the perfusion pressure for good cerebral autoregulation is 60-120 mm Hg. Despite the fact that during chronic arterial hypotension mean blood pressure rare falls lower than 60 mm Hg, blood flow in the medial cerebral artery anyway impairs. As a result, subcortical regions and significant parts of the frontal, parietal and temporal lobes re-

ceive less arterial blood supply with appearance of above-mentioned symptoms.

Pathophysiological basis for the treatment of arterial hypotension:

- Correct management of the underlying disorder;
- Nonpharmacological methods: compression of veins in the lower extremities to enhance venous return to the heart; drink of fluid up to 480 ml one time; physical activity; consumption of NaCl (1-2 g three times per day);
- Pharmacological therapy: use of synthetic mineralocorticoids, α_1-agonists and cholinesterase inhibitors.

PART III. PATHOPHYSIOLOGY OF THE RESPIRATORY SYSTEM

Main function of the respiratory system is to provide gas exchange between alveolar air and blood in the pulmonary capillaries. For normal pulmonary gas exchange it is necessary for normal activity of all mechanisms participating in this process: (1) normal regulation of respiration; (2) adequate alveolar ventilation; (3) adequate perfusion of pulmonary alveoli with blood; (4) normal diffusion of O_2 and CO_2 through alveolar and capillary wall. Impairment of these processes may lead to any abnormalities of the respiratory system.

Disorders of respiration regulation

Coordinated respiratory movements result from rhythmical discharge from interconnected neurons in the reticular substance of the brainstem (respiratory center). Respiratory center receives impulses from chemical and mechanical sensors. Chemical sensors (chemoreceptors) are classified into peripheral and central. Peripheral chemoreceptors are located in the peripheral vasculature (carotid bodies, located at the bifurcation of the common carotid arteries and the aortic bodies near the arch of the aorta). Central chemoreceptors are in the brainstem. Breathing is stimulated by a fall in the PaO_2, a rise in the $PaCO_2$, or an increase in the hydrogen ion concentration of arterial blood. Mechanical sensors involve a number of receptors. Pulmonary stretch receptors are placed in airway smooth muscle and mucosa; their afferent fibers are carried in the vagus nerve. They discharge in response to lung distention. Increasing lung volume decreases the rate of respiration by increasing expiratory time (Hering-Breuer reflex). Unmyelinated C-fibers are located near the pulmonary capillaries (that is why they are called as juxtacapillary J-receptors). These fibers stimulate the respiratory drive during interstitial edema or pulmonary fibrosis. Proprioceptors in joints, muscles, and tendons have some role in the increased ventilation during exercise. Muscle spindle receptors in the diaphragm and intercostals provide feedback on muscle force and they may be involved in the sensation of dyspnea. Motor discharges from the respiratory center travel via the phrenic and intercostal nerves to the respiratory musculature.

Disorders of respiration regulation manifest by bradypnea, tachypnea, apnea, dyspnea, periodic respiration, terminal respiration, cough, sneeze, and Kretschmer's reflex.

Bradypnea is an infrequent respiration, which is resulted from abnormal impulsing from chemoreceptors or mechanoreceptors to the respiratory center or from primary damage of respiratory motor neurons. As a reflex, bradypnea is seen during elevation of the BP (due to reflex from the baroreceptors located in the arch of the aorta) and during hyperoxia (after shutdown of "hypoxic drive"). Bradypnea with increased amplitude of respiration may be detected in patients with elevated resistance to the airflow in the upper respiratory airways. Such respiration is called as stenotic respiration. It caused by abnormal impulses from mechanoreceptors of

intercostal muscles and by Hering-Breuer reflex. Impaired activity of central chemoreceptors (in patients with coma, selected drugs or narcotics exposure, after brain trauma, hemorrhage, cerebral edema, etc.) may also result in bradypnea.

Tachypnea is a frequent breathing. It may be shallow or deep; physiological (during physical activity) or pathological. The latter is common during fever, hysteria, different pulmonary or cardiovascular diseases, pain, anemia, and metabolic acidosis. On the one hand, tachypnea serves as an adaptive reaction which permits to adapt pulmonary ventilation to oxygen demand or to compensate metabolic acidosis; but on the other hand, it decreases efficacy of respiration via decrease in effective respiratory volume instead of expansion of dead space volume. Moreover, uncontrolled tachypnea may lead to respiratory alkalosis and hypocapnia with secondary depression of the respiratory center.

Apnea is a temporary stop of breathing results from disorder of any level of the respiratory control system. Two forms of potentially life-threatening apnea were described.

Central sleep apnea (CSA) is characterized by a lack of drive to breathe during sleep, resulted in insufficient or absent ventilation and compromised gas exchange. There are two basic pathogenetic variants of central sleep apnea: (1) with impaired central drive ("won't breathe") and (2) with impaired respiratory motor control ("can't breathe").

Etiology of CSA with impaired central drive includes different pathologic conditions. Tumors of brainstem structures may directly diminish ventilatory output. Rare congenital central hypoventilation syndrome (formerly known as the Ondine curse) is characterized by significant alveolar hypoventilation during sleep. Ventilatory responses and sensations of dyspnea to hypercapnia and hypoxia are often absent or greatly diminished in such children. The breathing pattern during sleep is characterized by near-normal respiratory rate with decreased tidal volume. Severe hypercapnia and hypoxemia lead to secondary polycythemia, pulmonary hypertension, and cor pulmonale. Impaired central respiratory drive is impaired also by opioid-containing medications. Obesity-induced hypoventilation syndrome, which is partially caused by an abnormal leptin signaling in such individuals, also is an example of impaired central respiratory drive.

Impaired respiratory motor control is seen in hypercapnic patients with primarily intact central respiratory output. However, these individuals have abnormalities from upper motor neurons right down the neuromotor axis to the respiratory muscles. Causes include wide range of neuromuscular disorders: myasthenia gravis (defects in neuromuscular junction), amyotrophic lateral sclerosis (motor neuron disease), post-polio syndrome, and myopathies. Chest wall syndromes such as kyphoscoliosis can also be associated with hypoventilation and CSA.

Obstructive sleep apnea (OSA) is characterized by recurrent episodes of upper airway obstruction, and is associated with reductions in ventilation, resulting in recurrent arousals and episodic oxyhemoglobin desaturations during sleep. The presence of soft tissues and bony structures, which increase extraluminal tissue pressures surrounding the upper airway, can predispose the pharynx to collapse. In

contrast, the actions of pharyngeal dilator muscles maintain pharyngeal patency due to reflex pathways from the CNS and within the pharynx. The presence of these opposing forces suggest that increased pharyngeal collapsibility is due to alterations in anatomically imposed mechanical loads and/or in dynamic neuromuscular responses to upper airway obstruction during sleep. Such anatomical changes include tonsillar hypertrophy, retrognathia, and variations in craniofacial structures thus increasing upper airway collapsibility. Obesity links with elevations in neck circumference and increased amounts of peripharyngeal fat, which could narrow and compress the upper airway. The compressive effects of fatty tissue deposited around the pharynx therefore may increase upper airway collapsibility, and possibly offset the effects of dilator muscles that maintain airway patency. Obesity may also increase pharyngeal collapsibility through reductions in lung volumes, particularly decreases in functional residual capacity, which are accentuated with the onset of sleep. Clinical consequences of the disorder cover a wide spectrum including daytime hypersomnolence, neurocognitive dysfunction, cardiovascular disease (arterial hypertension – See Fig. 2-32, stroke, myocardial infarction, and heart failure), metabolic dysfunction, respiratory failure, and cor pulmonale. The major risk factors for the disorder include obesity, male gender, postmenopausal status, and age.

Dyspnea (from Greek “dys” and “pnea”) means “disordered breathing”. The American Thoracic Society defines it as “a subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity.” Dyspnea may be induced in four distinct settings: (1) increased ventilatory demand such as with exertion, febrile illness, hypoxic state, severe anemia, or metabolic acidosis; (2) decreased ventilatory capacity such as with pleural effusion, pneumothorax, intrathoracic mass, rib injury, or muscle weakness; (3) increased airway resistance such as with asthma or chronic obstructive pulmonary disease; and (4) decreased pulmonary compliance such as with interstitial fibrosis or pulmonary edema. Dyspnea may develop in patients with heart failure or due to psychogenic causes (anxiety, panic disorders).

To better understanding pathogenesis of dyspnea it is important to know basic principles of respiration regulation. Afferent signals, efferent signals, and central information processing are active participants of this process. Afferent signals are sensory neuronal signals that ascend to the brain. Afferent neurons significant in dyspnea arise from a large number of sources including the carotid bodies, medulla, lungs, and chest wall. Chemoreceptors in the carotid bodies and medulla supply information regarding the blood gas levels of O_2, CO_2 and H^+. In the lungs, juxtacapillary (J) receptors are sensitive to pulmonary interstitial edema, while stretch receptors signal bronchoconstriction. Muscle spindles in the chest wall signal the stretch and tension of the respiratory muscles. Thus, poor ventilation leading to hypercapnia, left heart failure leading to interstitial edema (impairing gas exchange), asthma causing bronchoconstriction (limiting airflow) and muscle fatigue leading to ineffective respiratory muscle action could all contribute to a feeling of dyspnea. Efferent signals are the motor neuronal signals descending to

the respiratory muscles. The most important respiratory muscle is the diaphragm. Other respiratory muscles include the external and internal intercostal muscles, the abdominal muscles and the accessory breathing muscles. As the brain receives its plentiful supply of afferent information relating to ventilation, it is able to compare it to the current level of respiration as determined by the efferent signals. If the level of respiration is inappropriate for the body's status then dyspnea might occur. There are several explanations of pathogenesis of dyspnea. According with "length - tension inappropriateness theory," which was proposed by the basic defect in dyspnea is a mismatch between the pressures (tension) generated by respiratory muscles and the tidal volume (change of length). Whenever such disparity occurs, the muscle spindles of the intercostal muscles transmit signals that bring the act of breathing to the conscious level. Additionally, juxtacapillary receptors (J-receptors), located in the alveolar interstitium and supplied by unmyelinated fibers of the vagus nerve, are stimulated by pulmonary congestion. This activates the Hering-Breuer reflex whereby inspiratory effort is terminated before full inspiration is achieved, resulting in rapid and shallow breathing. The J-receptors may be responsible for dyspnea in situations where pulmonary congestion occurs, such as with pulmonary edema. Other mechanisms of dyspnea include activation of chemoreceptors due to acid-base imbalance, central nervous system mechanisms, decreased breathing reserve, increased work of breathing, increased transpulmonary pressure, fatigue of respiratory muscles, and increased oxygen cost of breathing, dyssynergy of intercostal muscles and the diaphragm, and abnormal respiratory drive.

Dyspnea may be inspiratory (difficulties in inhalation), expiratory (difficulties in exhalation) or mixed. Inspiratory dyspnea is detected in patients with diffuse parenchymal pulmonary disease, whereas expiratory dyspnea is most common in patients with obstructive pulmonary diseases.

Periodic and terminal types of breathing are illustrated in the Fig. 3-1. Cerebral hypoperfusion from any cause may result in alternating periods of hyperventilation and apnea called **Cheyne-Stokes respiration**, although no breathing difficulty may be perceived by the patient. Other causes of such periodical breathing include hypoxia, heart failure, encephalitis, meningitis, injections of morphine. It also may develop in premature infants and in some healthy adults during deep sleep. Basically, Cheyne-Stokes respiration is resulted from impaired sensitivity of neurons in the respiratory center to CO_2. The latter results in the periodically developing apnea with accumulation of CO_2 and arterial hypotension with subsequent activation of chemoreceptors and baroreceptors, accordingly, followed with restoration of activity in neurons in the respiratory center and breathing with sinusoid-like amplitude.

Cerebral lesions or intracranial hemorrhage may be associated with intense hyperventilation and sometimes irregularly periodic breathing called **Biot's respiration**. Amplitude of respiratory movements is constant. Mechanisms of Biot's respiration are similar to those in Cheyne-Stokes respiration.

Terminal breathing develops in terminal states and includes Kussmaul's respiration, apneistic respiration and gasping-respiration. Diabetic ketoacidosis sel-

dom causes dyspnea but commonly induces slow, deep respirations termed **Kussmaul's respiration**. It is noisy, deep tachypnea which may be frequent detected in patients with severe metabolic acidosis, especially following diabetic ketoacidotic coma. Mechanisms of Kussmaul's respiration are: metabolic acidosis → accumulation of H^+ in the blood → activation of chemoreceptors → stimulation of the respiratory center → positive ventilator drive → hyperventilation → decrease in pCO_2 in extracellular fluid → attempt to compensate metabolic acidosis.

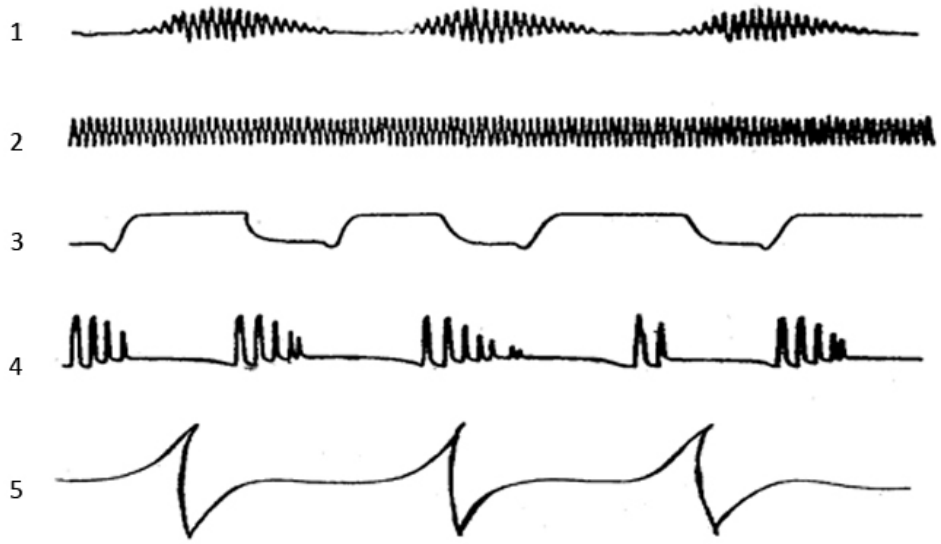


Figure 3-1. Periodic and terminal types of breathing

1 – Cheyne-Stokes respiration; 2 – Kussmaul's respiration; 3 – apneistic respiration; 4 – Biot's respiration; 5 – gasping-respiration.

Apneistic respiration is characterized by an impaired of inspiration-respiration alternation. Experimental apneistic respiration is reproduced after transection of both nerves vagus and brainstem between rostral part of the brain and its middle and caudal parts. Such transection results in permanent activity of the apneistic center.

Gasping-respiration is seen especially during death agony, for instance, in the terminal phase of asphyxia. Increased respiratory movements, which originate from excitations of neurons in the caudal parts of the brainstem after shutdown of superposed neurons, coexist with prolonged apnea.

Cough is a sudden and often repetitively voluntary or involuntary occurring defense reflex which helps to clear the large breathing passages from secretions, irritants, foreign particles and microbes. The cough reflex consists of three phases: an inhalation, a forced exhalation against a closed glottis, and a violent release of air from the lungs following opening of the glottis, usually accompanied by a distinctive sound. Etiology of cough includes infectious or non-infectious causes. In case of viral or bacterial infections cough helps to remove pathogens from respiratory airways, but may facilitate spreading of such infections among

healthy persons. Non-infectious causes of cough are irritation of airways by foreign bodies, allergens in atopic asthma, and components of tobacco smoke, air pollutants, and gastric juice in patients with gastroesophageal reflux. Cough is a frequent symptom in patients with post-nasal drip, chronic bronchitis, lung tumors, heart failure and medications such as ACE inhibitors. The cough reflex is initiated by stimulation of two different classes of afferent nerves, namely the myelinated rapidly adapting receptors, and nonmyelinated C-fibers with endings in the lungs.

Sneeze, or sternutation, is a semi-autonomous, convulsive expulsion of air from the lungs through the nose and mouth after irritation of the nasal mucosa. Sneezing is caused after sudden exposure to bright light, sudden fall in environmental temperature, exposure of cold air, or viral infection or allergens. The protective role of sneezing is to remove mucus containing foreign particles or irritants and cleanse the nasal cavity. During a sneeze, the soft palate and palatine uvula depress while the back of the tongue elevates to partially close the passage to the mouth so that air ejected from the lungs may be expelled through the nose. Because the closing of the mouth is partial, a considerable amount of this air is usually also expelled from the mouth. Mechanism of sneezing is following: interaction of triggers with nasal mucosa → release of histamine → irritation of the ending of the n. trigeminus → impulses pass in the brainstem along the ventromedial part of the spinal trigeminal nucleus and the adjacent pontine-medullary lateral reticular formation → efferent signals → activation of the pharyngeal and tracheal muscles → large opening of the nasal and oral cavities → sneeze.

Kretschmer's reflex was described in 1870 after irritation of upper airways with different chemical substances, for example, ammonia. Apnea, closure of glottis, bradycardia, fall of arterial pressure followed with its elevation are clinical signs of this protective reflex preventing damage of lower airways (including toxic pulmonary edema) by potentially dangerous evaporating irritants. Impulses from receptors in upper airways are transmitted by olfactory nerve, trigeminal nerve, and glossopharyngeal nerve.

Disorders of alveolar ventilation

Such disorders may be seen as most common alveolar hypoventilation and less common alveolar hyperventilation.

Alveolar hypoventilation

There are two types of alveolar hypoventilation – obstructive and restrictive.

Obstructive type of alveolar hypoventilation (in Latin "obstruction" means obstacle) is caused by a narrowing of airways or their obstruction in bronchial asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis and cystic fibrosis; (2) a plugging of respiratory airways with foreign body; (3) external compression of respiratory airways.

Spirometry is useful method for the detection of disorders of alveolar ventilation. Normal spirogram is presented in the Fig. 3-2.

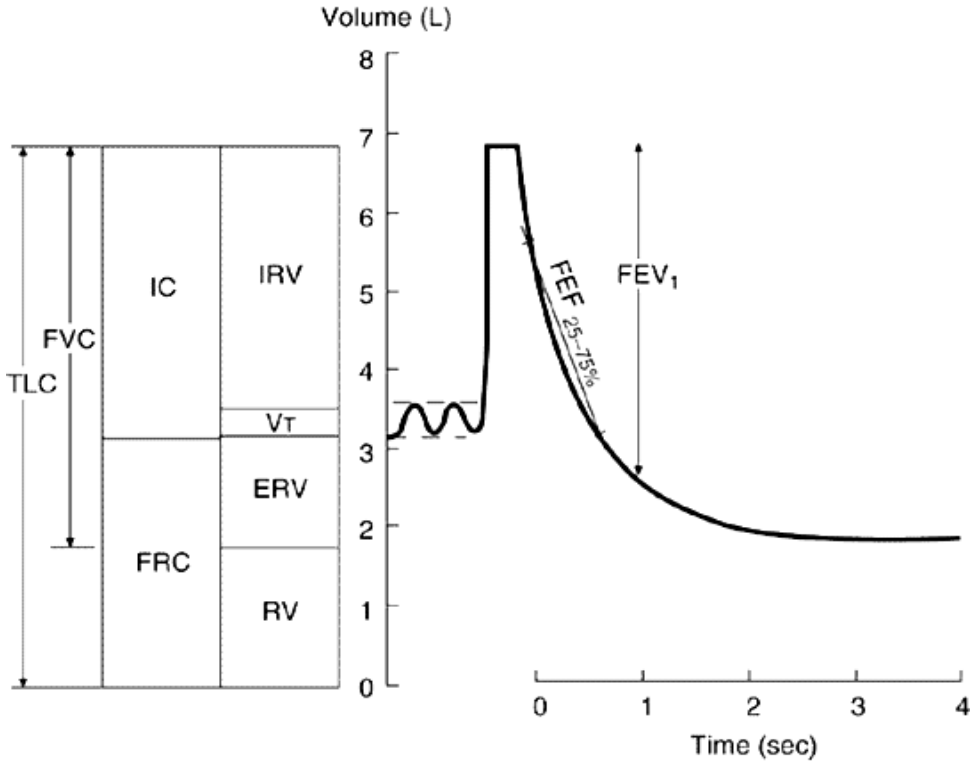


Figure 3-2. Normal spirogram

Tidal volume *(**V_T**) is the amount of gas inhaled and exhaled with each resting breath. A normal tidal volume in a 70-kg person is approximately 350–400 mL.*

Residual volume *(**RV**) is the amount of gas remaining in the lungs at the end of a maximal exhalation.*

*The **vital capacity** (**VC**) is the total amount of gas that can be exhaled after a maximal inhalation.*

*The vital capacity and the residual volume together constitute the **total lung capacity** (**TLC**), or the total amount of gas in the lungs at the end of a maximal inhalation.*

*The **functional residual capacity** (**FRC**) is the amount of gas in the lungs at the end of a resting tidal breath.*

*The **forced vital capacity** (**FVC**) maneuver begins with an inhalation from FRC to TLC (lasting about 1 second) followed by a forceful exhalation from TLC to RV (lasting about 5 seconds).*

*The amount of gas exhaled during the first second of this maneuver is the **forced expiratory volume in 1 second** (**FEV_1**). Normal subjects expel approximately 80% of the FVC in the first second.*

Obstructive type of alveolar hypoventilation is characterized by following changes of spirometric parameters (Fig. 3-3):

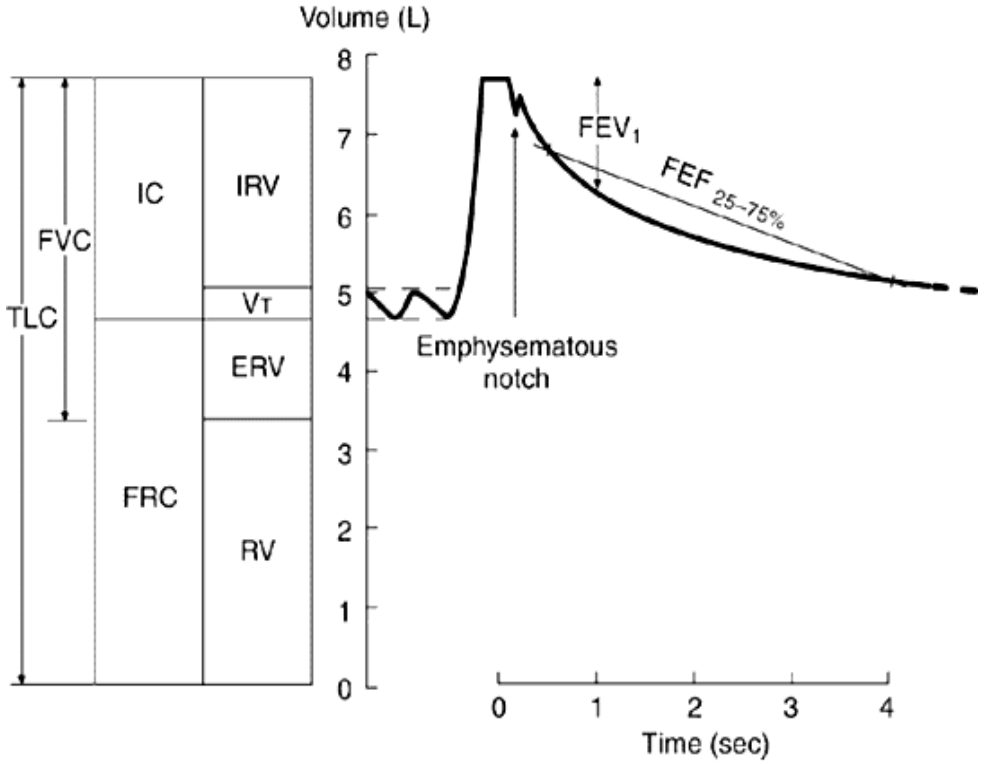


Figure 3-3. Spirogram in patient with obstructive type of alveolar hypoventilation

- All flow rates are decreased.
- FEV_1, FVC, and the FEV_1/FVC (FEV_1% ratio) are all reduced.
- Expiratory time prolongation, early airway closure caused by loss of elastic recoil and consequent air trapping produce increases in the RV and FRC.
- TLC is increased.

A selected form of the obstructive type alveolar hypoventilation is asphyxia. **Asphyxia** (from Greek "without" and "squeeze") is a potentially life-threatening condition of severely deficient supply of oxygen with development of generalized hypoxia, which is resulted from abnormal breathing. Causes of asphyxia include choking, constriction or obstruction of upper or lower airways (laryngospasm, obstruction by foreign bodies, bronchoconstriction in asthma), environmental causes where oxygen is not readily accessible, carbon monoxide inhalation, acute respiratory distress syndrome, intoxications (for example, with phosgene, which directly affects lungs, or cyanides), drowning, drug overdose with suppression activity of the respiratory center, hanging, self-induced hypocapnia after pulmonary hyperventilation, sleep or central apnea, generalized seizures, and acute respiratory distress syndrome (See later).

Acute asphyxia lasting 3-4 min. passes through three stages:

1. Excitation of the respiratory center due to accumulation of CO_2 in the blood. This stage is characterized by inspiratory dyspnea, deep and slightly hurried breathing, tachycardia and rise in blood pressure, which are resulted from

excitation of the vasomotor center in hypoxic condition. With time breathing slows down, expiratory dyspnea starts, generalized clonic convulsions and spontaneous defecation and urination develops. Initially excitation in the brain cortex succeeds by inhibitory processes with resultant unconsciousness.

2. Activation of parasympathetic nervous system and fall of excitability of the respiratory center caused by severe hypercapnia. Breathing slows to even complete apnea; bradycardia and arterial hypotension are registered.
3. Severe depression of the respiratory and vasomotor center. Reflexes are failed, pupils are dilated; blood pressure falls significantly, heart rate becomes rare but strong. Terminal respiration is followed by complete paralysis of respiratory center. Resuscitation is possible, when heart activity is preserved.

Restrictive type of alveolar hypoventilation (in Latin "restriction" is limitation) may be resulted from disease affecting pulmonary parenchyma (interstitial pulmonary diseases, pulmonary fibrosis, pulmonary edema) or other causes including neuromuscular diseases affecting respiration, phrenoplegia, myasthenia, muscular dystrophy, kyphoscoliosis, severe obesity, ankylosing spondylitis, etc. During this type of hypoventilation stretch of lung is impaired. Spirogram illustrated restrictive type of alveolar hypoventilation is presented in the Fig. 3-4.

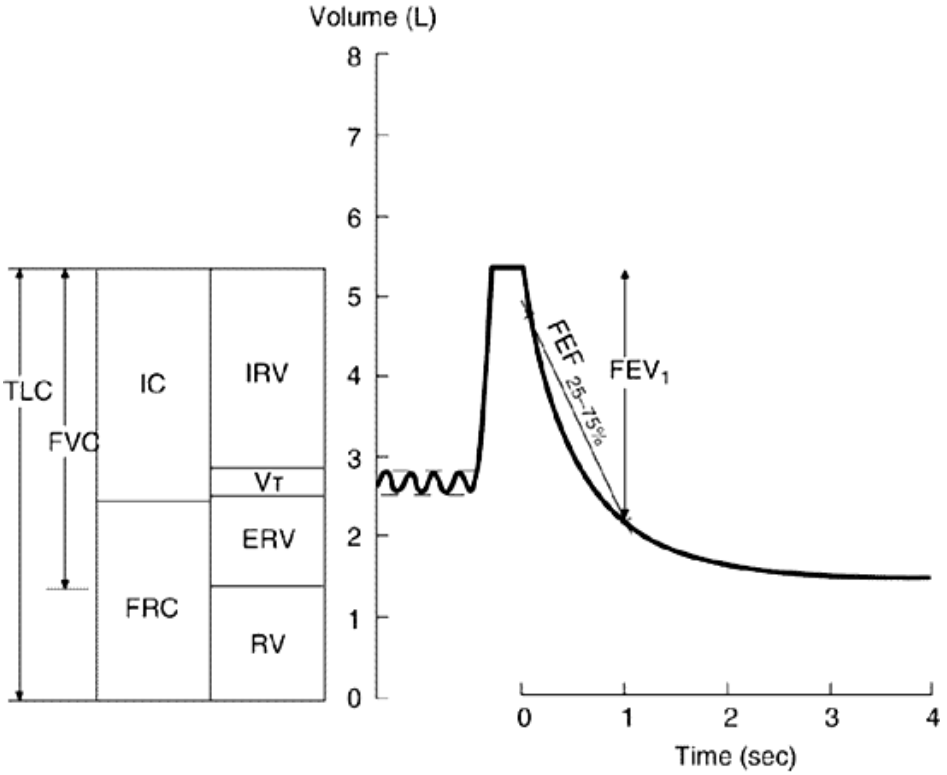


Figure 3-4. Spirogram in patient with restrictive type of alveolar hypoventilation

- TLC, FEV_1, and FVC are reduced;
- Ratio of FEV_1/FVC (FEV_1%) is normal or even increased.

Alveolar hypoventilation leads to the arterial hypoxemia, hypercapnia and respiratory acidosis (See Later).

Atelectasis as a cause of alveolar hypoventilation

Atelectasis is a pathologic state in where the alveoli are deflated with alveolar hypoventilation. The most common cause is post-surgical atelectasis, characterized by splinting, i.e. restricted breathing after abdominal surgery. Atelectasis implies some blockage of a bronchiole or bronchus, which can be within the airway (foreign body, mucus plug), from the wall (tumor, usually squamous cell carcinoma) or compressing from the outside (tumor, lymph node, tubercle). Another cause is poor surfactant spreading during inspiration, causing the surface tension to be at its highest which tends to collapse smaller alveoli. Atelectasis may also occur during suction, as along with sputum, air is withdrawn from the lungs.

Atelectasis may be an acute or chronic. There are several types of atelectasis according to their underlying mechanisms or the distribution of alveolar collapse; resorption, compression, microatelectasis and contraction atelectasis. Absorption (resorption) atelectasis occurs after pure oxygen inhalation. The oxygen may be absorbed into the blood, reducing the volume of the alveoli, resulting in a form of alveolar collapse. Compression (relaxation) atelectasis usually associates with accumulation of blood, fluid, or air within the pleural cavity, which mechanically collapses the lung. Leakage of air into the pleural cavity (pneumothorax) also leads to compression atelectasis. Chronic atelectasis may take one of two forms - middle lobe syndrome or rounded atelectasis.

Alveolar hyperventilation

It is resulted from severe stress, hysteric reactions, vomiting, damage of the CNS, hyperthermic syndromes, and pyretic and hyperpyretic fever. Inadequate regimen of the artificially pulmonary ventilation also may lead to the iatrogenic alveolar hypoventilation. Excessive exhalation of CO_2 leads to metabolic acidosis with subsequent cerebral vasoconstriction and global cerebral hypoperfusion. During respiratory alkalosis different compensatory reactions develop: H^+ begin to go out from red blood cells and bones, whereas K^+ enters into these cells. Such disturbance result in electrolyte disturbances, paresthesia, seizures, and cardiac arrhythmias. The oxyhemoglobin dissociation curve shifts to the left. This means that dissociation of oxyhemoglobin in the microcirculation will be impaired.

Ventilation-perfusion imbalance

Not all ventilated alveoli in normal condition receive equal amount of blood. The optimal ratio between ventilation and perfusion of alveoli with blood should be 0.8 – 1.0. This means that normal alveolar ventilation is approximately 4.5 l/min. and normal perfusion is approximately 5 l/min. Even in physiological conditions the distribution of ventilation and perfusion in different pulmonary zones is

not uniformly. Imbalance between ventilation (V) and perfusion with certain flow of blood per minute (Q) may lead to high or low V/Q ratio.

High V/Q ratio occurs when ventilation exceeds decreased perfusion with increase in alveolar dead space. Such situation may be seen in pulmonary thromboembolism or pulmonary vascular diseases (pulmonary arterial hypertension, vasculitis affecting pulmonary blood vessels), massive pulmonary vasoconstriction as an example of compensatory reaction following severe acute hemorrhage, dehydration or shock, or in DIC, and sludge of blood cells in the pulmonary microvasculature. High V/Q ratio is not associated with increase in blood oxygenation; however, relatively normal blood oxygenation can be maintained by activation of chemoreceptors and tachypnea. Tachypnea may lead to hypocapnia. High V/Q ratio associates with increase in work of breathing with subsequent tiredness of respiratory muscles.

Low V/Q ratio results from (1) decrease in pulmonary ventilation; (2) increase in perfusion of alveoli. Causes of alveolar hypoventilation were discussed earlier. Arterial hypoxemia in low V/Q ratio will lead to the hypoxic pulmonary vasoconstriction (Von Euler's-Liljestrand's reflexes). In response to low PaO_2 in the alveolar air to 60-70 mm Hg vasoconstriction of pulmonary arterioles is started. This increases resistance to blood flow and redistributes flow in regions with higher PaO_2 in the alveolar air. Low V/Q ratio sometimes originates from the blood shunting. Right-to-left shunting means direct fault of the venous blood in the arterial system without coming in contact with alveolar gas (anatomic shunt). Shunting may occur also in atelectatic alveoli or alveoli filled with fluid (alveolar shunt). Low V/Q ratio associates with hypoxemia and hypercapnia.

Pulmonary arterial hypertension as a cause of abnormal pulmonary perfusion

Pulmonary arterial hypertension (PAH) is a stable increase in blood pressure in the system of the pulmonary artery above 25 mm Hg at the rest and above 30 mm Hg during physical exercises. Pulmonary arterial hypertension can be classified into primary and secondary. According with level of injury, PAH can be subdivided into precapillary (which is most severe), capillary, and postcapillary. Secondary PAH complicates different diseases and pathologic states:

- Systemic diseases of the connective tissue affecting pulmonary blood vessels;
- Portal hypertension (so-called hepatopulmonary syndrome);
- Heart (valvular) diseases with volume overload of the left atrium and/or left ventricle via the following mechanism: rise of the end-diastolic pressure in the LV → rise of the end-diastolic pressure in the LA → increase resistance to the blood flow in the pulmonary arteries (Kitaev's reflex);
- Pulmonary vascular disorders (capillary hemangiosis, veno-occlusive pulmonary disease, persistent PAH of newborns);

- Pulmonary diseases associated with alveolar hypoxemia (COPD, diffuse parenchymal lung disease, residence of highland) due to hypoxic pulmonary vasoconstriction;
- Pulmonary thromboembolism;
- Musculoskeletal disorders with chronic alveolar hypoventilation;
- Disturbances of respiratory control (See before);
- Rare miscellaneous causes.

Primary pulmonary arterial hypertension can be diagnosed in patient after exclusion of above-listed causes. Hereditary predisposition plays an important role in the pathogenesis of the primary PAH. Gene mutations or stable epigenetic marks strongly associate with primary PAH. Such affected genes include BMPR2 (encoding TGF-β), KCNK3 (encoding pH-sensitive potassium channel in vSMCs in the pulmonary vasculature), CAV1 (encoding caveolin-1, a protein which forms complex with endothelial NO-synthase in endothelial cells in pulmonary vasculature). At least 7 mutated genes-candidates were proposed as a significant cause of the primary PAH. The disease is most common among females indicating a definite role of sex hormones. Additional factors, such as use of some anorectics, psychostimulants, toxic oils and HIV infection may increase risk of primary PAH.

Small blood vessels (with diameter <500 microns) in the pulmonary artery system are damaged during PAH. Increase of their flow resistance is due to: (1) pulmonary vasoconstriction; (2) proliferation of vSMCs; (3) formation of microtrombi (Fig. 3-5).

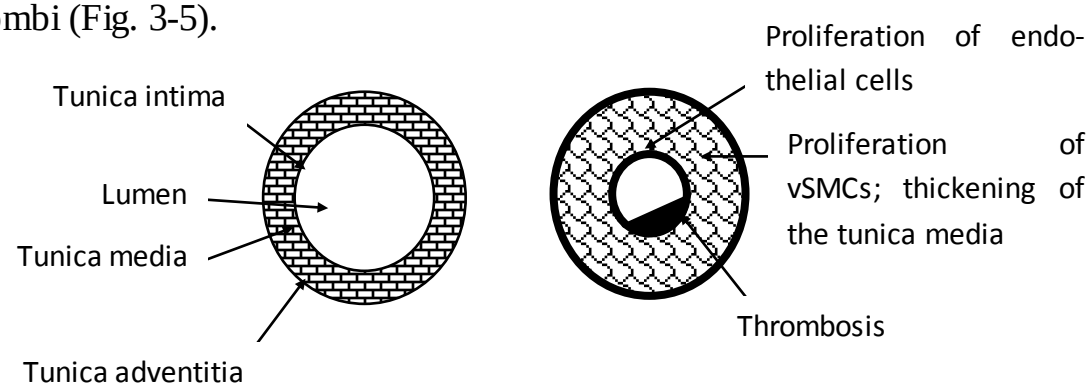


Figure 3-5. Remodeling of small pulmonary vessels following pulmonary arterial hypertension

Pulmonary vasoconstriction results from disbalance between vasoconstrictors (↑ production of endothelin-1, angiotensin II, thromboxane A_2, serotonin) and vasodilators (↓ synthesis and/or bioavailability of NO, prostacyclin, adrenomedullin, vasointestinal peptide, etc.). Some vasoconstrictors also act as a growth-promoting factors leading to the hypertrophy of tunica media of small pulmonary vessels. Decreased expression of potassium ion channels (Kv1.5 and Kv1.2) in the

pulmonary vSMCs results in their depolarization, accumulation of intracellular Ca^{2+}, vasoconstriction and proliferation. Genetically-based local hyperproduction of TGF-β is responsible for collagen and matrix deposition in the vascular wall, stimulation of chemotaxis of leukocytes, activation of cellular proliferation and their differentiation in the vascular wall, induction of apoptosis of vascular cells, and activation of proteolytic enzymes thus leading to the vascular remodeling. Microthrombi plug lumen of pulmonary vessels increasing resistance to the blood flow. Thrombosis is caused by endothelial dysfunction, inflammation in the vascular wall and blood flow disturbances in the pulmonary circulation.

Increase in resistance to the blood flow in the system of pulmonary arteries leads to pressure overload of the right ventricle with its isometric hyperfunction and concentric hypertrophy with development of right-sided and then total heart failure. Patients with PAH suffer from dyspnea, severe hypoxemia and congestive heart failure during late stages of the disease.

Pathophysiologic basis for treatment of PAH. Traditional therapy includes:

- Antagonists of L-type of calcium channels to reduce resistance to the pulmonary blood flow as an initial therapy;
- Warfarin to decrease blood coagulation and prevent thrombosis;
- Oxygenotherapy to ameliorate hypoxemia;
- Prostacyclin and its analogues (iloprost and treprostinil) to induce pulmonary vasorelaxation;
- Endothelin receptors antagonists (bosentan, ambrisentan, etc.) to abolish pulmonary vasoconstriction;
- Phosphodiestase-5 inhibitors (sildenafil and analogues) do decrease degradation rate of cGMP – a second messenger of NO-induced vasodilation;
- Soluble guanylate cyclase activators (riociguat);
- Heart and lung transplantation in advanced stages of disease.

Novel methods for the treatment of PAH are under investigation now. They involve stimulation of vasodilation, prevention of vascular remodeling and suppression of inflammation in the pulmonary circulation. New approaches are: elastase inhibition, Kv channel openers, statins, PPARγ agonists, growth factors receptors inhibitors, adrenomedullin, Rho-kinase inhibitors, cyclosporine, and endothelial progenitor cells with activated endothelial NO-synthase.

Disorders of gases diffusion through the alveolar-capillary membrane

Normally gases O_2 and CO_2 should pass through thin layer of a fluid on the surface of alveolar cells, alveolar cells, connective tissue fibers, endothelial cells, serum and membrane of RBCs (Fig. 3-6). Diffusion rate of O_2 and CO_2 through alveolar-capillary membrane depends on different factors: (1) gradient of pO_2 and pCO_2 in the alveolar air and in the blood; (2) diffusion area of the alveolar-capillary membrane; (3) diffusion capacity of the alveolar-capillary membrane and its thickness; (4) solubility of O_2 and CO_2.

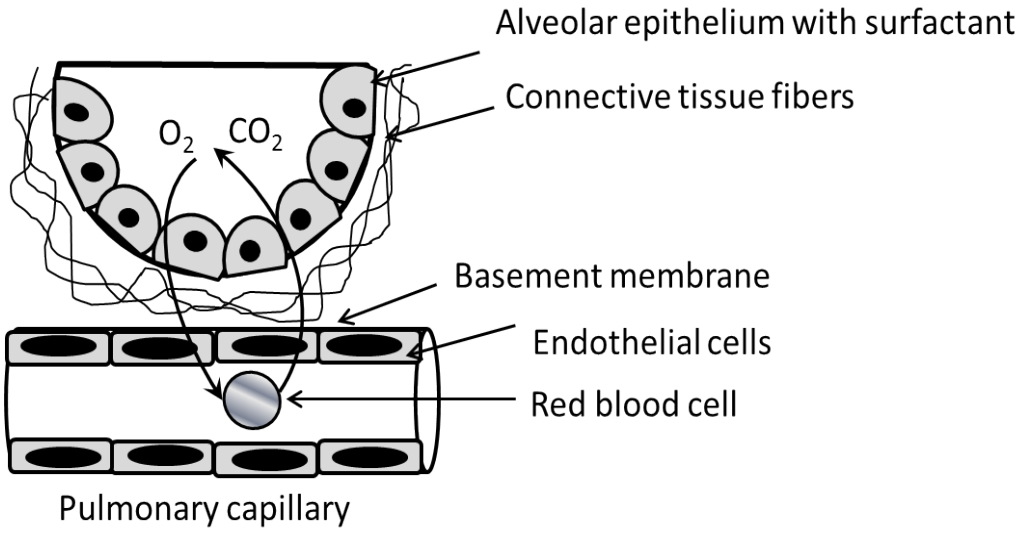


Figure 3-6. Schematic representation of gases diffusion in the lungs

Despite the fact that disorders of gases diffusion through the membrane may increase or decrease, the latter disorder is most common. An increase in diffusion rate of O_2 and CO_2 may be detected in healthy young persons (before 20 years), in tall men in horizontal position and during physical exercises. Causes of decrease in gases diffusion in the lungs are schematically presented in the Fig 3-7.

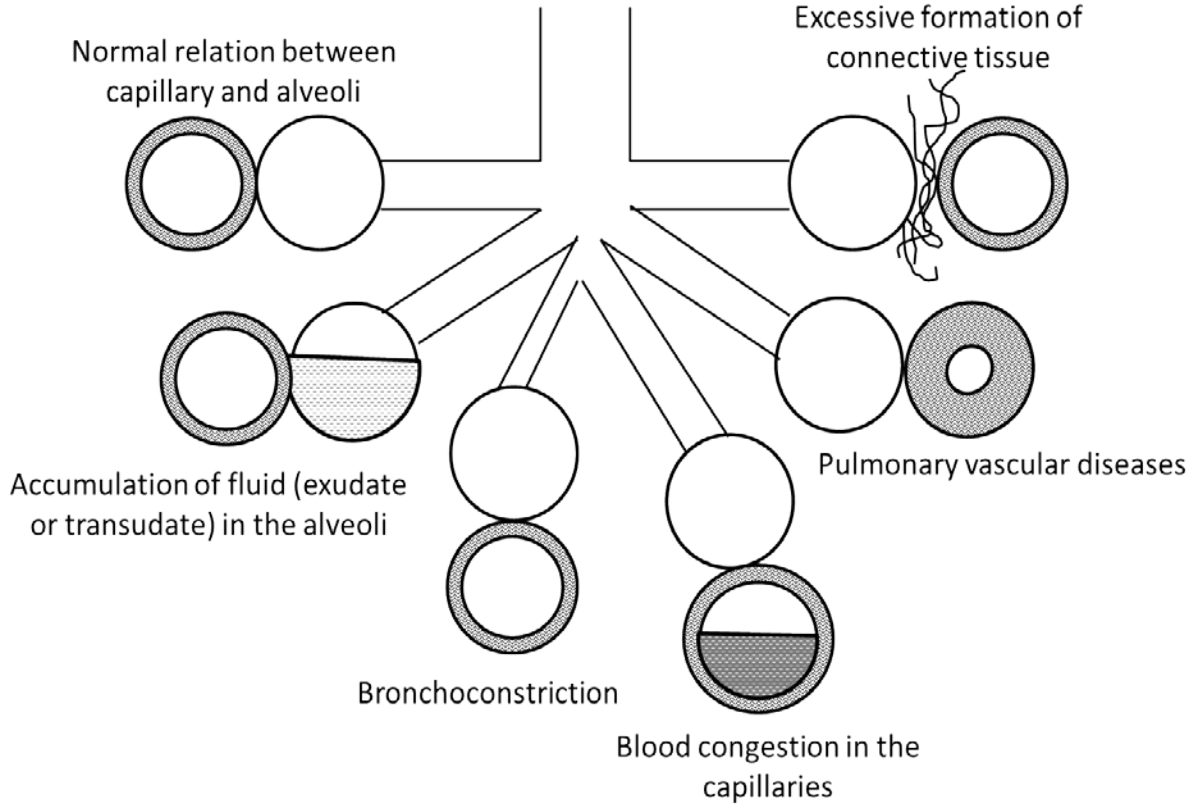


Figure 3-7. Pathogenetic variants of impaired gases diffusion through the alveolar-capillary membrane

Decrease in gases diffusion through the membrane may be physiological (in individuals older than 20 years) or pathological. Pathological decrease in gases diffusion is seen in patients with pneumonia or alveolar pulmonary edema, because of accumulation of any fluid in the alveoli increases diffusion distance for O_2 and CO_2. Pulmonary emphysema which is characterized by an excessive destruction of alveolar septum, leads to decrease in diffusion area. Diffuse parenchymal lung diseases result in interstitial edema, pulmonary fibrosis, loss of pulmonary capillaries and ventilation-perfusion mismatch. Vasculitis is also characterized by impairment of gases diffusion. All above-mentioned pathologies may lead to the respiratory failure and commonly manifest by hypoxia, but not hypercapnia, because diffusion rate of CO_2 is 20-25 folds greater than diffusion rate of O_2.

Pulmonary edema as a cause of abnormal gases diffusion through the alveolar-capillary membrane

In physiologic conditions, fluid and protein leakage occur primarily through small gaps between capillary endothelial cells. Fluid and solutes that are filtered from the circulation into the alveolar interstitial space do not enter the alveoli because the alveolar epithelium is composed of very tight junctions. Filtered fluid enters the alveolar interstitial space, and moves into the peribronchovascular space. Normal lymphatics remove most of this filtered fluid from the interstitium and return it to the systemic circulation. Movement of larger lung microcirculation is approximately equal to the hydrostatic pressure in the pulmonary capillaries, which is partially offset by a protein osmotic pressure gradient.

Accumulation of a fluid in the pulmonary interstitium or in the alveoli is termed as pulmonary edema. Interstitial edema causes dyspnea and tachypnea. Alveolar flooding leads to arterial hypoxemia and may be associated with cough and expectoration of frothy edema fluid. According with basic pathogenetic mechanism, pulmonary edema is classified into cardiogenic pulmonary edema (also termed hydrostatic or hemodynamic edema) and noncardiogenic pulmonary edema (also known as increased-permeability pulmonary edema).

Cardiogenic pulmonary edema is due to myocardial ischemia, exacerbation of chronic systolic or diastolic heart failure, and dysfunction of the mitral or aortic valve. Volume overload often predisposes to cardiogenic pulmonary edema. Pathogenesis of cardiogenic edema: left-sided heart failure → increased left ventricular end-diastolic pressure and left atrial pressure → elevated pulmonary venous pressure → mild increased hydrostatic pressure in the pulmonary capillaries (18-25 mm Hg) → increased transvascular fluid filtration with edema in the perimicrovascular and peribronchovascular interstitial spaces → progression of heart failure → increased of left atrial pressure more than 25 mm Hg → edema fluid breaks through the lung epithelium, flooding the alveoli. Patients with cardiogenic pulmonary edema should be treated with diuretics and afterload reduction, although the underlying cause may require other treatment, including coronary revascularization.

Noncardiogenic pulmonary edema is caused by an increase in the vascular permeability of the lung (which is seen in pneumonia, sepsis, aspiration of gastric contents, and major trauma associated with the administration of multiple blood-product transfusions, allergens or toxins exposure, DIC, acute pancreatitis), resulting in an increased flux of fluid and protein into the interstitium and air spaces. Noncardiogenic pulmonary edema has higher protein content because the vascular membrane is more permeable to the outward movement of plasma proteins. Patients with noncardiogenic pulmonary edema who require mechanical ventilation should be ventilated with a positive end-expiratory pressure. It is necessary to correctly treat underlying disorder.

Respiratory failure

Respiratory failure is a pathologic syndrome characterized by decrease of PaO_2 below to 60 mm Hg and increase of $PaCO_2$ over 46 mm Hg, on the understanding that patient takes atmosphere air under normal barometric pressure (E.J.M. Campbell, 1965). In other words, respiratory failure is a condition characterized by inability of the organism to maintain PaO_2 and $PaCO_2$ in the normal range or when respiratory system do so with increased efforts or with artificial ventilation.

Etiology of respiratory failure is following:

- Disorders of neural and/or humoral pulmonary ventilation;
- Diseases of musculoskeletal system affecting thorax;
- Diseases affecting lower and upper respiratory airways, as diseases affecting parenchyma of lungs;
- Disorders of systemic or pulmonary hemodynamic.

There are different principles of classification of respiratory failure:

I. According with rate of development:
   - Acute, developing following several minutes and life-threatening (for example, after obstruction of upper airways with foreign body, acute toxic pulmonary edema, penetrating wound of the thorax);
   - Chronic, developing slowly and persisting even several years or decades.

II. Depending on results of gas composition of the arterial blood:
   - Hypoxemic (PaO_2 <60 mm Hg and $PaCO_2 \leq 40$ mm Hg), developing in case of low oxygen concentration in the inhaled air, in alveolar hypoventilation, ventilation-perfusion imbalance, shunting of the blood and low saturation of arterial blood with oxygen;
   - Hypoxemic-hypercapnic (PaO_2 <60 mm Hg and $PaCO_2$>46 mm Hg), which develops during late stage of alveolar hypoventilation, and inadequate pulmonary perfusion combined with relatively normal pulmonary ventilation.

Acute hypoxemia results in the number of pathological signs, such as tachycardia, tachypnea, anxiety, diaphoresis, altered mental status, confusion, cyanosis, arterial hypotension or hypertension, bradycardia in advanced prolonged hypoxemia, seizures, coma and lactic acidosis. Acute hypercapnia leads to the somnolence, lethargy, restlessness, tremor, slurred speech, headache, asterixis, papilledema, coma and diaphoresis. Fall of arterial pH less than 7.3 may lead to the pulmonary vasoconstriction and generalized peripheral vasodilation. Increased myocardial excitability predisposes to fatal arrhythmia. Hypercapnia, decrease in pH of arterial blood and accumulation of 2,3-biphosphoglycerate in RBCs shift curve of dissociation of oxyhemoglobin to the right. This compensatory reaction helps to improve releasing of oxygen in the microcirculation. Chronic hypoxemia triggers corresponding responses on different integrative levels (See Part VII in the Textbook "General pathophysiology: the essentials"). Respiratory failure often manifests by dyspnea.

Acute respiratory distress syndrome as a cause of acute respiratory failure

Acute respiratory distress syndrome (ARDS) is an acutely developing diffuse damage of pulmonary parenchyma, which is resulted from increased permeability of the alveolar-capillary membrane, thrombosis of pulmonary microvessels and disorders of surfactant metabolism with development of severe uncontrolled inflammation and marked hypoxemia. The disorder is a complication of different pathologies with direct or indirect lung injuries:

- Direct injury (pneumonia, inhalation of toxic substances, contusion of lungs, aspiration of gastric juice, near-drowning);
- Indirect injury (sepsis, shock of any etiology, severe trauma, multiple transfusions, acute pancreatitis).

Natural history of ARDS reflects stages of acute inflammation (Fig. 3-8).

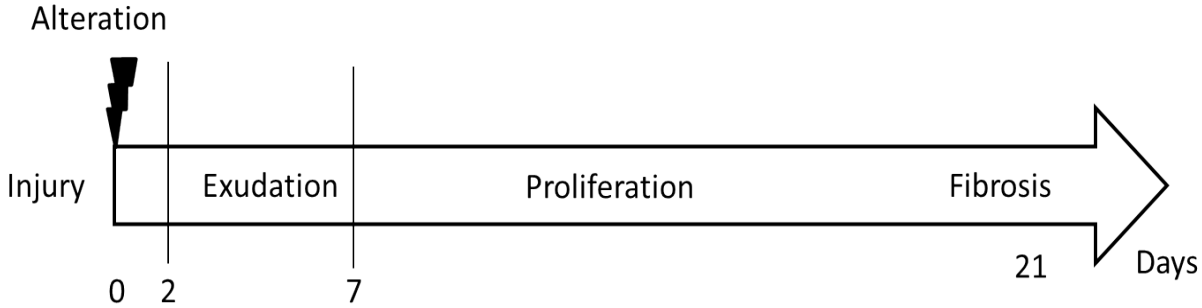


Figure 3-8. Time course of the development of ARDS

ARDS progresses following four stages:

1. Initiation;
2. Amplification;
3. Phase of injury;
4. Phase of recovery.

Pathogenesis of ARDS schematically is illustrated in the Fig. 3-9.

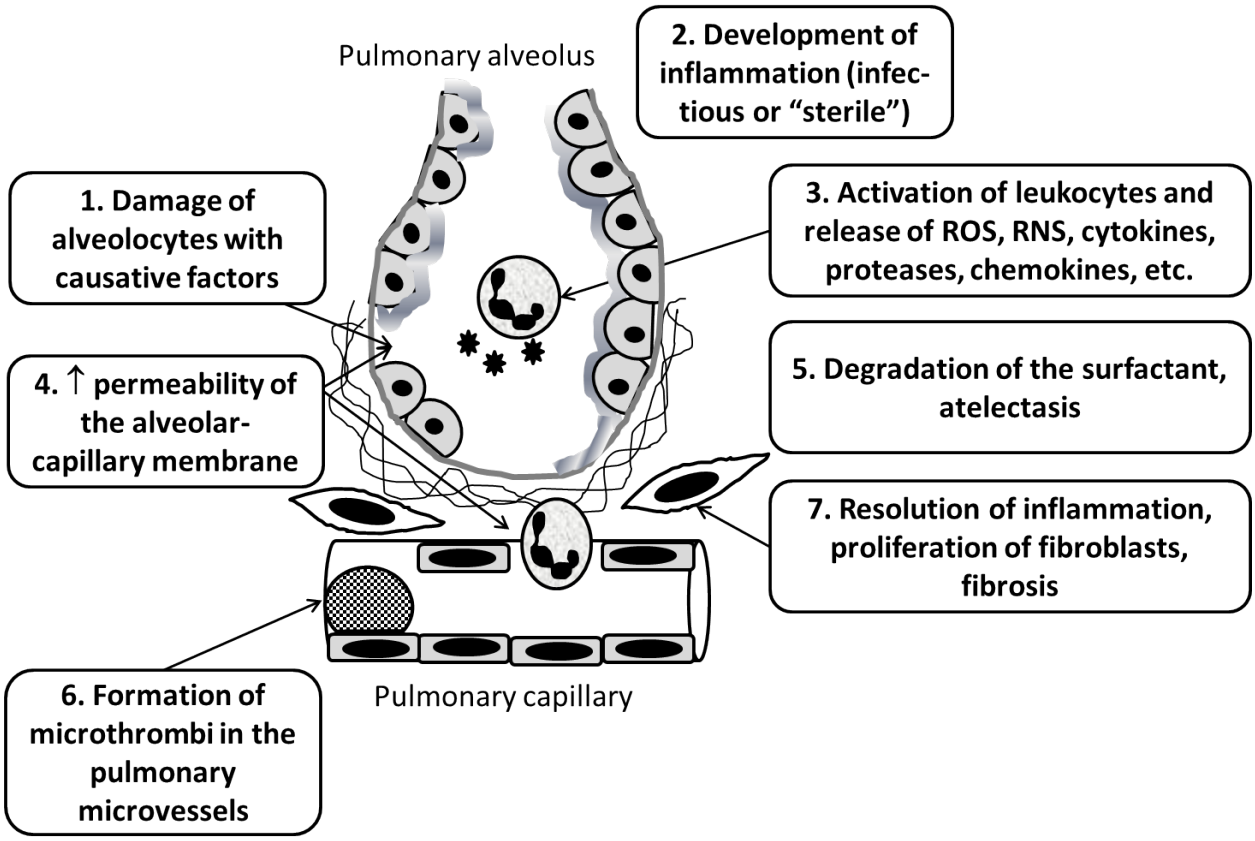


Figure 3-9. Simplified mechanisms of ARDS

Initiation phase is caused by DAMPs or PAMPs depending on the cause of inflammation. These products stimulate different subsets of leukocytes, alveolar epitheliocytes, smooth muscle cells, endotheliocytes and stromal cells to produce inflammatory mediators. Both cellular-derived and humoral inflammatory mediators cause secondary injury thus supporting inflammation (amplification phase). Leukocytes release ROS, RNS, proinflammatory cytokines, chemokines, and proteases. Such mediators damage alveolocytes. Dying of alveolocytes (from necrosis and apoptosis) and increased vascular permeability leads to formation of edema fluid, which accumulates in the interstitial spaces and in alveoli. Damage of alveolocytes type II impairs surfactant synthesis, whereas proteolytic enzymes degrading it. Loss of surfactant causes multiple atelectasis of alveoli. Hyaline membranes consisting from fibrin and components of extracellular matrix are formed. Endothelial injury results in thrombosis (a kind of DIC) in the pulmonary microcirculation. All these processes lead to inappropriate pulmonary ventilation, disorders in pulmonary perfusion and disorders of gases diffusion through the alveolar-capillary membrane with development of acute respiratory failure, and severe hypoxemia. Multiple organ dysfunction syndromes complicate ARDS leading to high mortality which is approximately 70%.

Adequate therapy and timely activation of an endogenous program of inflammation resolution lead to the resorption of exudate, phagocytosis of cellular

debris by macrophages, reprogramming of these cells to alternatively activated macrophages (M2), synthesis of proresolving molecules, proliferation of alveolocytes and restoration of surfactant synthesis (phase of recovery). However, in case of extreme injury restoration of the pulmonary parenchyma is achievable only after activation of fibroblasts and synthesis of extracellular matrix with excessive fibrosis. Such pulmonary fibrosis is a cause of restrictive-type of alveolar hypoventilation and chronic respiratory failure.

Infant respiratory distress syndrome (**IRDS**), also called neonatal respiratory distress syndrome, is a syndrome in premature borne infants caused by developmental insufficiency of surfactant production and structural immaturity in the lungs. It can also be a consequence of neonatal infection. The peak of incidence reaches in babies born at 26–28 weeks. Pathogenesis of IRDS is similar to those in ARDS.

Pathophysiologic basis for treatment of ARDS are: (1) adequate treatment of underlying disorders; (2) mechanical pulmonary ventilation with positive end-expiration pressure; (3) maintaining of a normal or even low left atrial filling pressure; (4) suppression of extreme inflammatory reaction with glucocorticoids and other anti-inflammatory drugs; (5) surfactant replacement; (6) correction of DIC and multiply organ dysfunction.

Pneumothorax as a cause of respiratory failure

The thoracic cavity is the space inside the chest with lungs, heart, and major blood vessels in it. A pleural membrane covers the surface of lung (visceral pleura) and also lines the inside of the chest wall (parietal pleura). A small amount of lubricating serous fluid is between these two layers. The lungs are fully inflated within the cavity because the pressure inside the airways is higher than the pressure inside the pleural space. Despite the low (negative) pressure in the pleural space, air does not enter it because there are no natural connections to an air-containing passage, and the pressure of gases in the bloodstream is too low for them to be forced into the pleural space.

A **pneumothorax** (from Latin “pneumo” – air and thorax) is a pathological accumulation of air in the pleural space causing collapsed lung and thus leading to the respiratory failure. Pneumothorax can be classified into primary, which occurs without underlying pulmonary disorders, and secondary, which associates with preexisting pathology (chronic obstructive pulmonary disease (COPD), infections, affecting lungs, interstitial pulmonary diseases, lung cancer, connective tissue diseases or endometriosis in females). However, patients with primary pneumothorax may have a genetic predisposition – risk of primary pneumothorax is greater in patients with diseases associated with increased fragility of the connective tissue – Marfan syndrome, Ehlers-Danlos syndrome, α_1-antitrypsin deficiency (which leads to emphysema).

According with etiology, pneumothorax may be traumatic (both iatrogenic and non-iatrogenic) or spontaneous. Depending on types, it can be classified into open, closed and tension pneumothorax (Table 3-1).

Table 3-1. Pathophysiologic characteristic of different types of pneumothorax

Types	Causes	Pathogenesis	Backgrounds for the treatment
Open	Stab or bullet wounds of the chest	Constant communication between pleural cavity and atmospheric air; the pleural cavity pressure=the atmospheric pressure	Covering of wound with an airtight seal
Closed	Rupturing of bullae (large air-containing lesions) in cases of severe emphysema; areas of necrosis of the lungs' parenchyma	Once air has stopped entering the pleural cavity, it is gradually reabsorbed. The pleural cavity pressure<the atmospheric pressure	Small spontaneous pneumothoraxes do not always require treatment, as they are unlikely to proceed to respiratory failure or tension pneumothorax, and generally resolve spontaneously.
Tension	Trauma of the thorax with formation of a one-way valve	The amount of air in the chest increases markedly; the pleural cavity pressure>the atmospheric pressure. Positive pressure in the pleural cavity impairs venous return to the heart. Increasing the respiratory rate (caused by activation of chemoreceptors, pulmonary stretch receptors, J-receptors) leads to a tiredness of respiratory muscles. Tachycardia is a response to hypoxia. Acute respiratory and cardiovascular failure may lead to death.	Urgent needle decompression of the pleural cavity

Pathophysiologic characteristic of obstructive respiratory diseases

Diseases with obstructive type of pulmonary hypoventilation include asthma, bronchiectasis, and chronic obstructive pulmonary disease (COPD). The latter consists of chronic bronchitis with predomination injury of terminal bronchioles, and pulmonary emphysema. Obstruction of lower airways in these pathologies is caused by common universal mechanisms (Fig. 3-10):

- Bronchoconstriction;

- Mucus hypersecretion or obstruction of lumen of bronchi with purulent exudate;
- Edema and infiltration of lower airways with small caliber with inflammatory cells;
- Remodeling of bronchial tree
- Loss of peribronchial support.

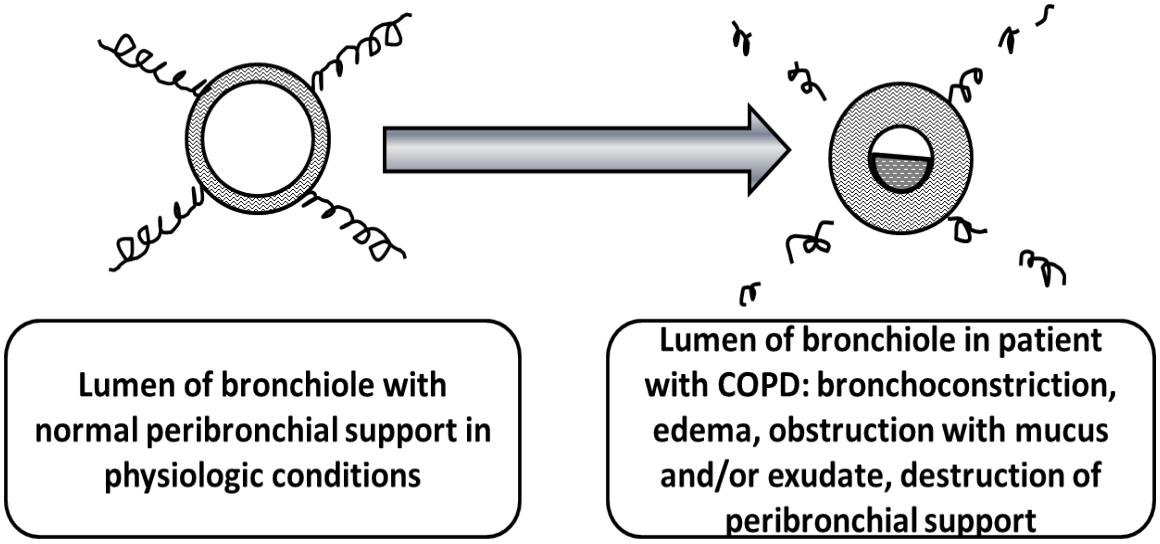


Figure 3-10. Mechanisms of airflow obstruction in obstructive pulmonary diseases

Chronic obstructive pulmonary disease is a multifactorial chronic progressing disease causing irreversible airflow obstruction and systemic changes. At least 1-2% of patients with COPD often have genetic predisposition, for instance, α_1-antitrypsin deficiency. α_1-antitrypsin, which is a serine protease inhibitor that is secreted into the circulation from the liver, is thought to protect lung tissue against digestion by neutrophil elastase and related serine proteinases. Other causes of disbalance proteases/their inhibitors were proposed as a cause of pulmonary emphysema. Environmental factors include smoking, air pollution, job hazard, and viral and bacterial infections affecting bronchial tree. In response to components of tobacco smoke, air pollutants (which trigger "sterile" inflammation), or infection ("infectious" inflammation) mucous glands and goblet cells in the airway epithelium begin to secrete mucus. CD4+, CD8+, and B-cells accumulate in the bronchial tree. The small distal airways (with diameter < 2mm) are most important site of injury and main cause of obstruction in COPD. As a result of chronic low grade inflammation in the upper airways, fibrosis is triggered, as like as a squamous cell metaplasia of bronchial epithelial cells. Obstruction of lumen of terminal bronchioles leads to the obstructive type of pulmonary hypoventilation and hypoxemia, which stimulates pulmonary hypoxic vasoconstriction. Functional vasoconstriction coexists with reduction of pulmonary vasculature due to fibrosis thus creating rise of resistance to the blood flow to the left ventricle with development of the "cor pulmonale".

Pulmonary emphysema often combines with chronic obstructive bronchitis. Pulmonary emphysema is characterized by abnormal distension of air space distal to terminal bronchioles, which is caused by destruction of supporting connective tissue. There are several types of pulmonary emphysema:

1. Centriacinar emphysema is most common, especially among smokers. It affects mostly central parts of acinus.
2. Panacinar emphysema is not frequent as centriacinar; it is characterized by an injury of all acinus.
3. Emphysema bullosa is seen in patients with α_1-antitrypsin deficiency. Macroscopically, lungs are likely to bunch of grapes.

Pathogenesis of pulmonary emphysema is illustrated in the Fig. 3-11.

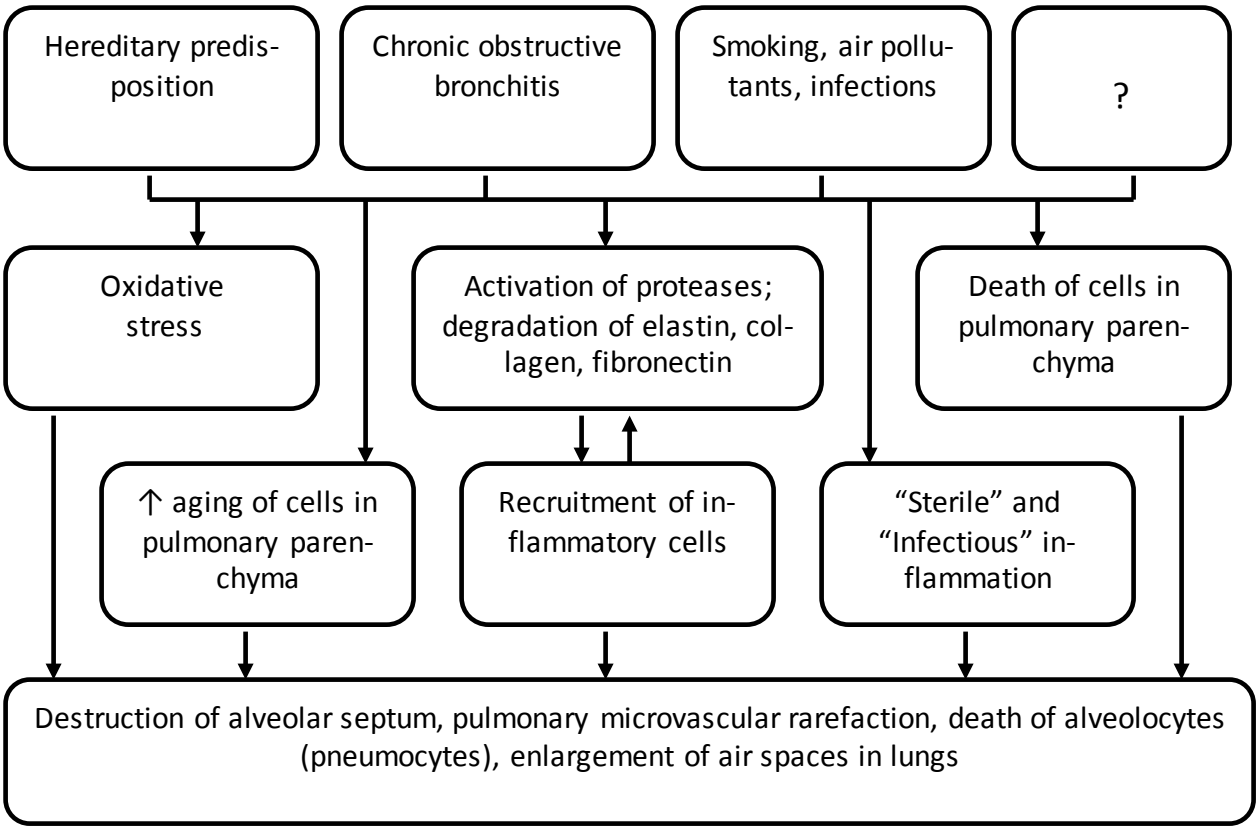


Figure 3-11. Pathogenesis of pulmonary emphysema

Smoking is an important exogenous factor promoting development of emphysema in patients with chronic obstructive bronchitis. It is explained by multiple mechanisms:

- Components of tobacco smoke accelerate apoptotic-induced death of cells in the pulmonary parenchyma;
- Recognition of apoptotic bodies by macrophages in smokers is impaired; this favors formation of "neoantigens" triggering autoimmune reactions and chronic inflammation in lungs;
- Components of smoke activate APCs with subsequent activation of cytotoxic T-cells, injury of pulmonary parenchyma, and perpetuation of inflammation;

- Oxidative and nitrozative stress in smokers causes cell injury and inflammation, with subsequent activation of neutrophils and releasing proteolytic enzymes degrading fibers of connective tissue;
- Acrolein, a component of tobacco smoke, leads to epigenetic modifications of a number of genes in lung cells, following with their premature death and changes of phenotype;
- Components of tobacco smoke impair synthesis of VEGF in pulmonary endotheliocytes. As a consequence, endothelial cells progressively dying, whereas neoangiogenesis is impaired. These causes lead to microvascular rarefaction in lungs;
- Components of tobacco smoke and other air pollutants inactivate proteases inhibitors thus leading to predomination activity of proteases and degradation of pulmonary extracellular matrix.

Exacerbations of COPD are commonly caused by infections affecting respiratory airways (Fig. 3-12).

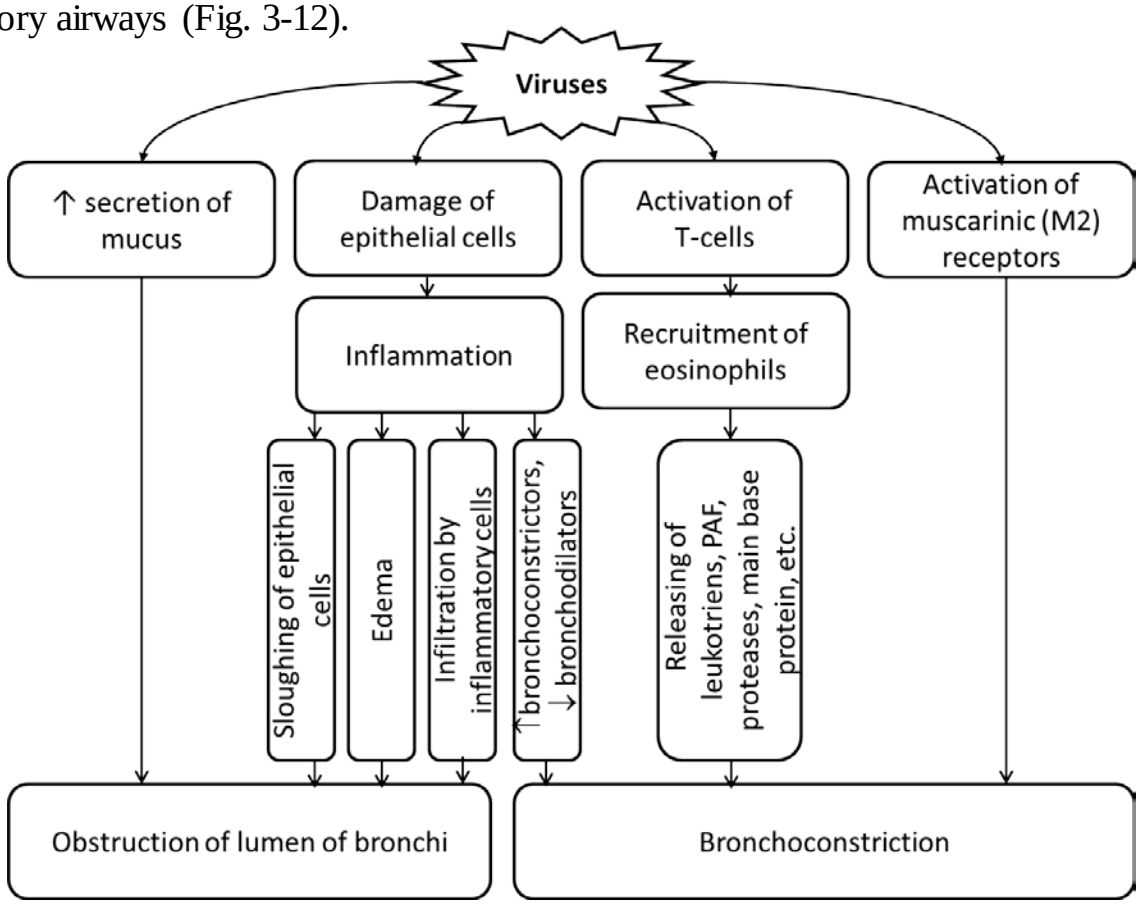


Figure 3-12.Role of respiratory viral infections in the pathogenesis of COPD exacerbation

Air pollutants (sulfur oxides, nitrogen oxides, ozone, products of fuel blowing) may also cause exacerbations of COPD.

Obstruction of bronchioles lead to delayed expiration with dynamic increase in air space. Dynamic elasticity of lungs decreases; dysfunction of respiratory muscles develops as a result of their tiredness. Alveolar hypoventilation clinically

manifests as change of patients' appearance. They look as or "pink puffers" or "blue bloaters". "Pink puffers" suffering from dyspnea, their gas exchange parameters are normal, inflammation in the bronchial tree is mild, emphysema is panacinar. "Blue bloaters" have severe inflammation in the lower airways and centriacinar emphysema; impaired gases exchange in lungs leads to hypoxemia and/or hypercapnia, and respiratory acidosis. These abnormalities are recognized by mechanoreceptors and chemoreceptors with stimulation of respiratory drive. However, tachypnea can't compensate disorders caused by bronchiolitis, obstruction of lower airways and emphysema. Increase in resistance to the blood flow in lungs worsening activity of cardiovascular system. "Cor pulmonale" is exhibited by right-sided cardiac hypertrophy and right-sided and heart failure (hypoxemia, blood congestion in vena cava superior and inferior, liver enlargement, severe edema, ascites). Respiratory and cardiovascular failure may lead to death. "Blue bloaters" also have secondary erythrocytosis.

Commonly COPD develops systemic complications (Table 3-2):

Table 3-2
Systemic complications of COPD

Complications	Pathogenesis
Features of systemic inflammatory response (leukocytosis, fever, synthesis of acute phase proteins in the liver)	Increases concentration of proinflammatory cytokines in the blood
Decrease in body mass, sometimes – cachexia	Rise in energy-expensive work of breathing, catabolic effects of TNF-α, decrease production of leptin
Poor exercise tolerance	Dysfunction of skeletal muscles in hypoxia, hypercapnia and acidosis, disbalance between anabolic and catabolic processes in the skeletal muscles, decrease in heavy chain myosin gene expression, excessive apoptotic death of muscle cells, induced by ROS, RNS and proinflammatory cytokines
Cardiac hypertrophy (right-sided or total), heart failure, arrhythmias	Pulmonary arterial hypertension, activation of the SNS, RAAS and side effects of β_2-adrenergic agonists, which are traditionally used in patients with COPD
Depression, disturbances of circadian rhythms	Dysfunctions of neurons in the CNS in hypoxic conditions
Osteoporosis	Muscles atrophy and abnormal activity of bone "mechanostat", sedentary lifestyle due to poor exercise tolerance, resorption of bone tissue in-

	duced by proinflammatory cytokines, negative influences of systemic glucocorticoid therapy on the bones
Edema	Activation of the SNS and RAAS complicated of chronic hypoxemia and hypercapnia; increase in vascular permeability; hypoproteinemia as a hallmark of cardiac liver cirrhosis and venous blood congestion in patients with right-sided or total heart failure
Secondary erythrocytosis	Hypoxemia-induced hyperproduction of EPO in the kidneys and stimulation of erythropoiesis in the bone marrow
Anemia	Anemia of chronic inflammation (chronic diseases), which is caused by hyperproduction of hepcidin in the liver in response to proinflammatory cytokines and decrease of availability of iron for the bone marrow

Pathophysiological basis for treatment of COPD. Etiotropic treatment includes smoking cessation, antibiotic therapy according with antibiotic sensitivity and/or antiviral drugs, and vaccination against influenza. For pathogenetic treatment several groups of drugs are recommended: (1) bronchodilators – β_2-adrenergic agonists, M-cholinergic antagonists, phosphodiesterase inhibitors; (2) anti-inflammatory drugs – inhalation glucocorticoids (or oral glucocorticoids to manage severe inflammation); (3) mucolytic agents; (4) oxygen therapy in patients with severe hypoxemia.

Asthma

Asthma is a multifactorial chronic inflammatory disease affecting conducting airways, which is characterized by a triad of signs:

1. Periodic obstruction of airways with different caliber, mainly with small caliber with expiratory dyspnea due to airflow limitation.
2. Bronchial hyperresponsiveness. Bronchial hyperresponsiveness is a qualitative and quantitative modulated response of bronchial smooth muscle cells to nonspecific stimuli (for instance, cold, perfume or subliminal concentrations of bronchoconstrictors).
3. Poor controlled inflammation in the airways.

In contrast to COPD, bronchial obstruction in asthma is not constant. It occurs, as a rule, only during attack of asthma. Obstruction can be relieved spontaneously or after administration of bronchodilators. Exacerbation of asthma may be induced by allergens, food additives, viruses, air pollutants and irritants, emotions, some unfavorable climatic conditions and in late lutein phase of the menstrual cycle in females related to progesterone deficiency.

Morphological picture of lungs presents by infiltration of bronchial tree with neutrophils, eosinophils and mast cells, thickening of the basement membrane in the pulmonary microvasculature, loss of intercellular contacts between epithelial cells, hyperplasia of goblet cells and obstruction of bronchial lumen with viscous sputum in asthma attack. Remodeling of bronchial tree demonstrates hyperplasia and/or hypertrophy of smooth muscle cells, proliferation of fibroblasts and deposition of extracellular matrix. Bronchial remodeling results in thickening of bronchial tree wall thus enhancing its hyperresponsiveness. The latter is augmented because of rate of hypertrophied muscular cells contraction becomes faster. Some patients with asthma demonstrate reflex bronchoconstriction, which is initiated by acetylcholine released from nerve ending. Such releasing is stimulated by different proinflammatory mediators.

Asthma is a multifactorial disease, which is originates as a combination of several causative factors, such as genetic predisposition, early developmental programming and environmental factors. According with mechanisms of it development, asthma can be subdivided into Th2-related (exogenous) and non-Th2-related (endogenous). To understand pathogenesis of Th2-related (atopic) asthma it is strongly recommended to revise Part XIII “Hypersensitivity reactions” in the Textbook “General pathophysiology: the essentials”.

Non-Th2-related endogenous asthma may manifest after physical exercises, inhalation of a cold air, after use of NSAIDs, β-adrenoblockers or after others nonspecific stimuli. Physical exercises stimulate of cooling and drying of epithelial bronchial cells with subsequent activation of mast cells and release from them potent bronchoconstrictors – histamine, prostaglandins and leukotrienes and reflex parasympathetic-mediated bronchoconstriction. Non-selective NSAIDs (especially aspirin and propionic acid derivatives) inhibit cyclooxygenase thus suppressing production of PGE_2. Metabolism of arachidonic acid is shifted towards lipooxygenase-dependent pathway with formation of powerful bronchoconstrictors – leukotriens. Asthma related with NSAIDs often coexists with nasal polyposis and chronic sinusitis. ACE inhibitors may provoke asthma, because they inhibit metabolic destruction of potent vasodilator bradykinin and lead to edema of bronchial wall. Repeated uncontrolled use of β-adrenergic agonists may lead to the severe complication of asthma – **asthmatic status.** Mechanisms of such influences are poorly understood; nevertheless, patients with asthma should avoid overdosage of β-adrenomimetics. Asthmatic status is characterized by ventilation-perfusion mismatch, severe hypoxemic or hypoxemic-hypercapnic respiratory failure, and acute respiratory acidosis.

Lung functions tests may be normal during remission or abnormal during asthma attack (See description of obstructive type of the alveolar hypoventilation in the present Part).

Pathophysiological basis for treatment of asthma. Main goal of asthma management is suggested (1) prevention correction of asthma attack; (2) treatment of asthma attack; (3) control of inflammation in the bronchial tree; (4) delay of bronchial tree remodeling. Different classes of drugs are used for this aim:

1. Bronchodilators:

A. Agonists of β_2-adrenergic receptors (albuterol, formoterol, salmoterol, etc.) are usually given as inhalation in asthma attack. They activate adenylate cyclase of bronchial smooth muscle cells with accumulation of cAMP and decrease concentration of Ca^{2+} with resultant bronchodilation.

B. Anticholinergic drugs (ipratropium, oxytropium) are administered as inhalation. They are selective antagonists of M_1 and M_3 cholinergic receptors, which are able to prevent histamine-induced bronchoconstriction and to cause bronchodilation.

C. Derivatives of methylxantines (theophylline) inhibit phosphodiesterase. As a result, accumulation of cAMP in bronchial muscle cells leads to bronchodilation.

D. Antileukotriene drugs or those which inhibit leukotrienes synthesis, or block receptors to leukotrienes (Fig. 3-13).

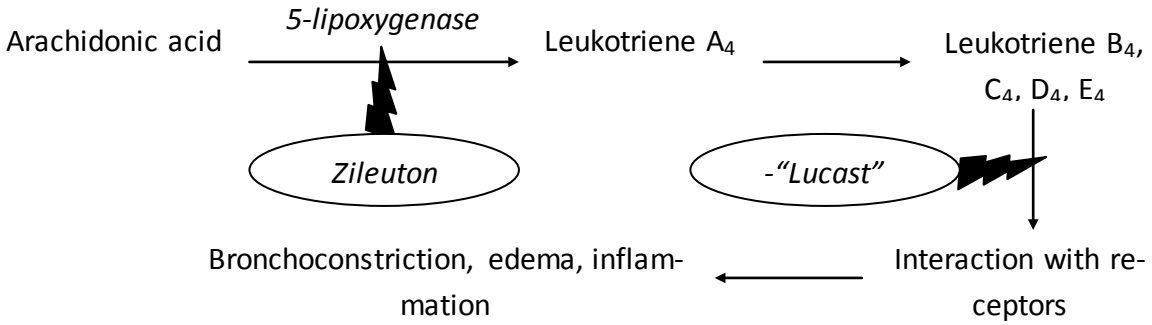


Figure 3-13. Point of action of antileukotrienes

2. Drugs which suppress inflammation in the airways

A. Glucocorticoids are administered locally with inhalation or in severe cases systemically per os or parenteral. Glucocorticoids act both genomically and non-genomically suppressing cellular and humoral immunity.

B. Drugs stabilizing mast cells membrane (disodium cromoglycate, nedocromyl sodium) block Cl-channels in the membrane of mast cells and prevent accumulation of Ca^{2+} in these cells. These drugs prevent, but not relieve asthma attack via prophylaxis of degranulation of mast cells. New groups of drugs, for example, antagonists of adenosine receptors are investigated now as stabilizers of mast cell membrane.

C. Drugs for immunotherapy.

Specific immunotherapy is recommended for patients with atopic asthma (See the Textbook "General pathophysiology: the essentials"). If it is impossible, for immunotherapy monoclonal antibodies against IgE (omalizumab) may be used. They prevent binding of IgE with high-affinity receptors to IgE on the surface of mast cells. Soluble anti-IL4 receptors, monoclonal antibodies against IL-13, IL-5 and TNF-α, antagonists of CCR chemokine receptors are under investigation now.

Selected pulmonary diseases with restrictive type of pulmonary hypoventilation

Pneumonia

Pneumonia is an acute inflammatory disease, which is caused by infectious agents (bacteria, viruses, fungi or pneumocystis) and affects pulmonary parenchyma with systemic inflammatory reaction. Normally different protective mechanisms provide sterility of upper airways. These mechanisms are: (1) regularly contraction of cilia of epithelial cells in upper respiratory airways and mechanical clearance of inspired air from pathogens in it; (2) protective reflexes – cough and sneeze; (3) innate immunity – macrophages, secretory IgA, lysozyme, interferon, complement, etc.; (4) adaptive immunity – specific lymphocytes and immunoglobulins. Insufficiency of protective mechanisms may lead to pneumonia.

Infectious pathogens may get into lungs via different pathways:

- Following aspiration of microorganisms (*Streptococcus pneumoniae, Streptococcus pyogenus, Mycoplasma pneumoniae, Haemophilus influenzae, Moraxella catarrhalis)* from the nasopharynx. Such aspiration is probable in individuals during sleep, especially after alcohol abuse or use of psychoactive substances. Patients with stroke, neurologic disorders, and general anesthesia or after placement of stomach pump may have aspiration of microorganisms. Absence of cough, disorders of mucociliary transport and poor activity of alveolar macrophages facilitate aspiration and related inflammation in the pulmonary parenchyma.
- After inhalation of mixed aerosols containing pathogenic microorganisms. A suspended particles of aerosols with diameter less than 5 microns containing the smallest droplets of saliva, mucus, and pathogens easy pass in the lungs. Such pathway is common for *Mycobacterium tuberculosis*, viruses, *Legionella* and some others pathogens affecting lungs.
- Hematogenous dissemination of infectious agents from extra pulmonary sites (for instance, dissemination of *Staphylococcus aureus* from damaged heart valves in endocarditis in the lungs).
- After direct contamination (following intubation of trachea or after penetrating wounds of the thorax).

Classification of pneumonia. Pneumonia can be classified into community-acquired and hospital-acquired (nosocomial). This principle of classification is used for correct therapeutic option. Nosocomial pneumonias may be caused by mixture of biological pathogens with drug resistance to definite number of antibiotics. Anatomically, pneumonia may be localized (lobar pneumonia) or diffuse (bronchopneumonia).

After appearance of infectious agents in lungs typical pathologic process – infectious process will be initiated (See Part X in the Textbook “General pathophysiology: the essentials”). Pathogen associated molecular patterns (PAMPs) and damage associated molecular patterns (DAMPs) are recognized by antigen present-

ing cells (See Fig. 9-1 in the Textbook “General pathophysiology: the essentials”). Primary injury due to direct pathogens exposure coexists with secondary injury, which is resulted from action of proinflammatory mediators. Microscopically, in pneumonia caused by *Streptococcus pneumonia* massive injury of alveolar epitheliocytes, extreme exudation with great amount of neutrophils and red blood cells in exudate, and consolidation of the pulmonary parenchyma are detected (so-called stage of “red hepatization”). Further, following approximately 2 days, macrophages are recruited in the inflamed lobe, which phagocytose necrotic debris and dying neutrophils. Exudate is removed via lympatic capillaries. This stage is called “grey hepatization”. Resolution of inflammation is followed by cellular regeneration and fibrosis of the pulmonary parenchyma.

Clinically, pneumonia manifests acutely with fever, malaise and signs of intoxication (See Acute phase response in the Textbook “General pathophysiology: the essentials”). These symptoms are followed with cough, pain in the thorax, and dyspnea. Some children and aging persons may develop acute respiratory failure due to alveolar hypoventilation.

Complications of pneumonia are: pleuritis, pleural empyema, pyothorax, bacteremia, SIRS, septic shock, ARDS, pulmonary abscess or carnification of the affected lung (extreme fibrosis).

Pathophysiological basis for the treatment of pneumonia: (1) etiotropic treatment depending on causative agent and sensitivity of microorganisms to antibiotics; (2) management of fever with NSAIDs; (3) correction of acute respiratory failure and intoxication; (4) physiotherapy during resolution stage.

Diffuse parenchymal lung disease

The term “diffuse parenchymal lung disease” (old term “interstitial pulmonary diseases) denotes a broad specter of pulmonary diseases, whose common feature is the infiltration of inflammatory cells and excessive formation of connective tissue in the lung parenchyma. Lung parenchyma, including alveoli, blood and lymphatic vessels, and perivascular space are affected. General pathogenesis of diffuse parenchymal lung disease is illustrated in the Fig. 3-14.

Morphologically, diffuse parenchymal lung disease can be subdivided into several groups:

- With predominant alteration of the lung parenchyma and pulmonary fibrosis. This group includes idiopatic interstitial pneumonia, aspiration pneumonia, inflammatory diseases in the lungs associated with diseases of connective tissue (systemic lupus erythematosus, rheumatoid arthritis, systemic scleroderma), fibrosing alveolitis in asbestosis, inspiration of inorganic pollutants, in adverse drug reactions - after use of antiarrhythmic drug amiodarone or cytostatic drugs, or in pulmonary hemosiderosis or amyloidosis.
- With advanced fibrosis and formation of cellular cysts, this is seen in idiopathic pulmonary fibrosis. It is a chronic disease with mild inflammatory reaction.

- With formation of granulomas in the pulmonary parenchyma. Granuloma looks as a round organized structure consisting from lymphocytes, macrophages and epithelioid cells with zone of necrosis in the center. Such type is observed in allergic pneumonitis resulted from inhalation of organic or inorganic dust, in sarcoidosis or granulomatous pulmonary vasculitis. Hypersensitivity reactions of III and IV types participate in such granulomatous pulmonary inflammation.

Excessive fibrosis decreases lung compliance causing restrictive pattern of alveolar hypoventilation (See Fig. 3-4). Thickening of alveolar wall and development of vasculitis results in an abnormal diffusion of gases through alveolar-capillary membrane. Such diseases also associate with ventilation-perfusion imbalance. As a result, arterial hypoxemia and dyspnea may develop, especially during physical exertion.

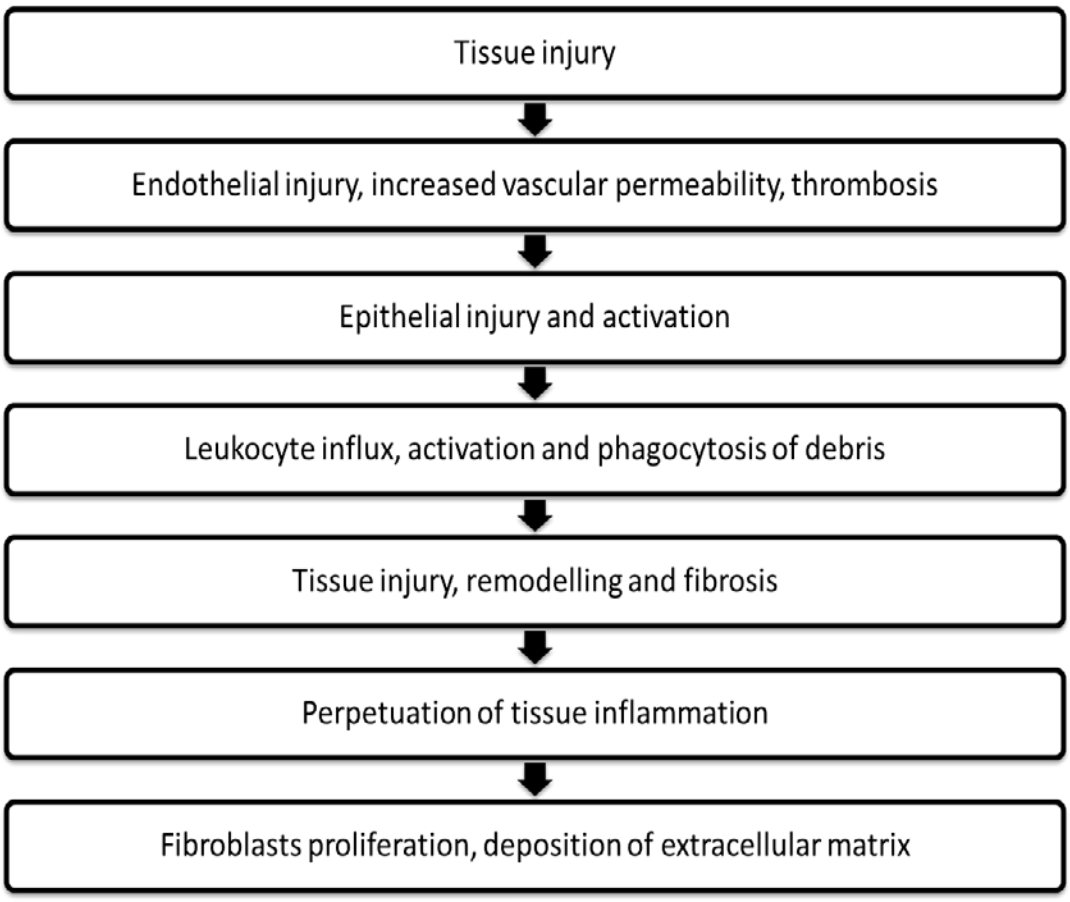


Figure 3-14. Simplified mechanisms of diffuse parenchymal lung disease

Pathophysiological basis for treatment of diffuse parenchymal lung diseases include suppression of inflammation and inhibition of extracellular matrix formation. Glucocorticoids and cytostatic drugs have variable efficacy that is why new agents are under investigation now: (1) agents modifying action of the TGF-β, which is able to stimulate fibroblasts and to trigger them to produce components of extracellular matrix; (2) anticytokine drugs; (3) antagonists of cellular adhesion molecules; (4) antagonists of chemokine receptors; (5) blockers of receptors on the

surface of fibroblasts; (6) stimulators of apoptotic death of fibroblasts; (7) monoclonal antibodies to VEGF to suppress neoangiogenesis; (8) inhibitors of prolylhydroxylase, an enzyme, participating in the synthesis and processing of collagen; (9) substances affecting balance between proteases and their inhibitors.

Non-respiratory functions of lungs and their disorders

For a joke, non-respiratory functions of lungs are illustrated in the Fig. 3-15.

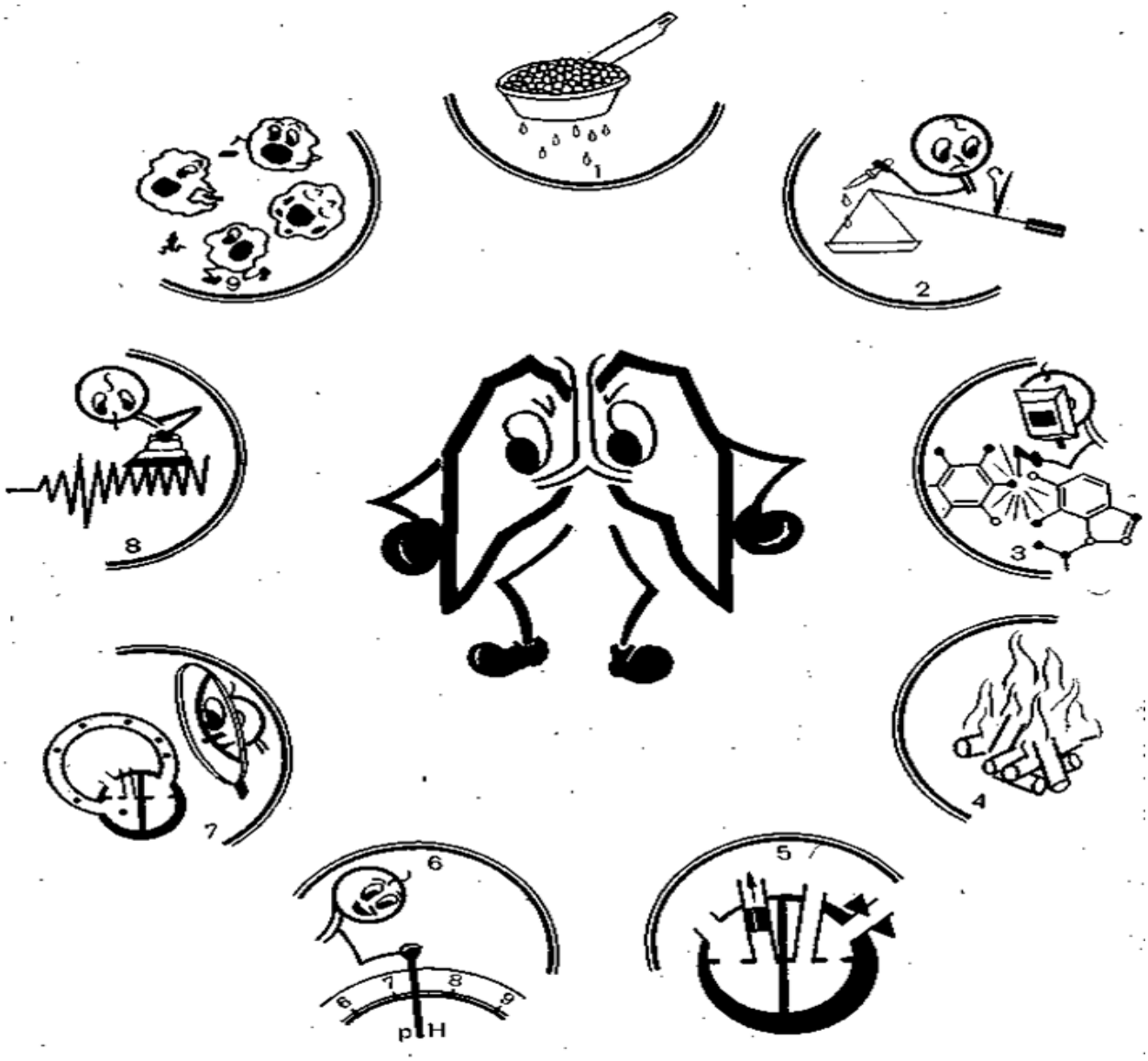


Figure 3-15. Non-respiratory functions of lungs

1 – clearance of the blood from admixtures (cellular aggregates, microemboli); 2 – regulation of balance of water and electrolytes; 3 – metabolism of lipids; 4 – thermoregulation; 5 – maintenance of hemodynamic balance between right and left parts of the heart; 6 – regulation of acid-base balance; 7 – metabolism of biologically active substances (hormones, kinins, prostaglandins, etc.); 8 – regulation of coagulant, anticoagulant and fibrinolytic system; 9 – immune defense.

Lungs are able to hold at least 90% of foreign particles with diameter more than 2 microns. Accumulated small particles with mucociliary clearance are removed with mucus from the organism. Smaller particles are ingested by alveolar macrophages and excreted from lungs with lymphatic flow. Lungs also excrete some volatile endogenous and exogenous metabolites (acetone, ammonia, alcohol, benzene) and degrade some xenobiotics. In contrast, certain part of lipid-soluble and water-soluble substances may be active absorbed by lungs. This fact explains usefulness of inhalations as an important pathway of drugs introduction in the organism.

With expired air some amounts of water loss, thus regulating balance of the water in the organism. Inspiration of cold air leads to activation of biological oxidation (for instance, β-oxidation of lipids) in the lungs with subsequent increase of heat production. In parallel, vasoconstriction of the pulmonary capillaries results in the diminished heat loss via lungs.

Lungs regulate influx of lipids in the blood, because they are able to metabolize some part of chylomicrons, which are transported in the lungs with lymph. Fatty acids and phospholipids, for example, main component of the surfactant, dipalmythoilphosphatydylcholine are synthetized in the lungs. Lungs are source of synthesis of proteins, especially elastin and collagen in the pulmonary parenchyma, as a net of proteins belonging to the innate immunity. Carbohydrates, especially components of mucus – mucopolysaccharides are also produced in the lungs. Due to their ability to let pass all blood, lungs inactivate some biological active substances in it, including bradykinin, serotonin, prostaglandins, and at least one third of total amount of norepinephrine and histamine. In the pulmonary vasculature ACE converts Ang I to the potent vasoconstrictor Ang II. Pulmonary mast cells contain heparin, and releasing of heparin prevents blood coagulation.

Disorders of these functions of lungs may provoke or maintain of disorders of different vital functions.

PART IV. PATHOPHYSIOLOGY OF THE GASTROINTESTINAL TRACT AND EXOCRINE PANCREAS

Basic functions of gastrointestinal tract include: (1) motor function; (2) secretory function; (3) digestion and (4) absorption. Functions of gastrointestinal tract are under control of the central and autonomic nervous system, humoral and endocrine substances. That is why there are multiple causes affecting gastrointestinal tract. Terminology describing symptoms of gastrointestinal diseases are listed in the Table 4-1.

Table 4-1. Gastrointestinal disorders: a short glossary

Term	Definition and characteristic
Aerophagia	Excessive unconscious swallowing of air with subsequent abdominal distension or bloating with improvement after belching. Results from disorders of motility of upper gastrointestinal tract or psychopathology
Anorexia	Complete loss of appetite, when hunger is absent and a patient has no desire to eat. A brief period of anorexia usually accompanies almost all acute diseases. Chronic anorexia usually occurs in people with a serious underlying disorder such as cancer; AIDS; chronic lung disease; and severe heart, kidney, or liver failure. Disorders that affect the part of the brain where appetite is regulated can cause anorexia as well. Anorexia is common among people who are dying. It may be drug-induced (digoxin, fluoxetine, quinidine, hydralazine).
Bulimia	A pathologic, sharply enhanced sense of hunger.
Constipation (obstipation)	A syndrome of a delay of defecation. May be mechanical, alimentary, toxic, neurogenic, endocrine and hypokinetic.
Diarrhea	Frequent defecation of loose, fluid, unformed stools
Dyspepsia	Persistent or recurrent epigastric pain or subjective upper abdominal discomfort (early satiety, postprandial fullness, bloating, nausea). Causes are: mucosal inflammation; impaired gastric acid secretion; disturbed motor and sensory function; CNS disorders, diet and environmental factors (drugs, smoking, alcohol, negative emotions, etc.)
Dysphagia	Difficulties in swallowing
Heartburn	A burning sensation in the substernal area or in the epigastrium that sometimes affects upward to the pharynx and even oral cavity, which is caused by reflux of the gastric juice to the esophagus
Hematemesis	Vomiting of blood
Hyperorexia	Abnormal hunger due to activation of the feeding center in the

	hypothalamus
Hyporexia	Decreased appetite with retention of demand for food, resulting from suppression of the feeding center and/or activation of the satiety center in the hypothalamus.
Malabsorption	A syndrome due to poor absorption of nutrients in the intestine
Melena	Blood in the stool
Polydypsia	Excessive thirst
Polyphagia	Eating an abnormally large amount of food

Diseases of the oral cavity

Dental caries

The oral cavity is the primary point of the digestive system. Main functions of oral cavity are: (1) food chewing; (2) lubrication of food; (3) assessing of food taste; (4) protective function.

Dental caries is a common multifactorial disease of dental tissues (enamel, dentine, cementum and pulp) causing their destruction. Several groups of factors participate in the development of caries:

1. Genetic predisposition. The major candidate gene categories include those which products participate in the enamel formation, immune response, saliva formation, taste formation and others.
2. Diet rich in refined carbohydrates, poor oral hygiene, hypovitaminosis of vitamin D, fluoride deficiency.
3. Oral microbial dysbiosis, which is characterized by predomination of pathogenic flora, mainly *Streptococcus species, Porphyromonas gingivalis*, etc. and formation of microbial biofilms. Biofilms are structured polymicrobial community containing more than 700 species of bacteria on oral surfaces.
4. Lack of factors preventing caries. Hyposalivation, deficiency of salivary antimicrobial proteins and peptides such as cystatins, histatins, lysozyme, lactoferrin, lactoperoxidase, defensins, cathelicidin and calprotectin, lack of fluoride and inadequate remineralisation of enamel as an insufficient biofilm control by immunity are responsible for the caries development.
5. Co-existing pathologies, including gastroesophageal reflux disease, hypoplasia of dental enamel, disorders of calcium and phosphorus metabolism accelerate demineralization of the enamel.

If pathological factors outweigh the protective factors, caries will develop. Microorganisms ferment dietary carbohydrates with formation of organic acids damaging dental tissues. However, periods of acid attack and mineral loss are interspersed with periods of remineralisation, and a cavity is formed only if mineral loss is greater than healing. Caries affects area of pits, fissures, and cervical parts of teeth where food retention occurs. Initially small spots on the enamel are formed (reflecting demineralization and loss of calcium and phosphates) with formation of caries cavity in the future. Once the lesion reaches dentine, pulpitis and necrosis of pulp tissues begin. Dentine caries may complicate with painful acute or chronic pulpitis, formation of apical granuloma and even apical abscess.

Pathophysiologic basis for the prevention of caries: (1) removal of dental biofilm with tooth brushing; use of toothpaste with antiseptics; use of probiotics; immunization; (2) reduction of dietary sucrose; (3) neutralization of acids within plaque; (4) remineralisation of the enamel with fluoride, vitamin D; (5) education and regular visits to a dentist.

Inflammatory periodontal diseases

Chronic gingivitis

Chronic gingivitis commonly affects adults and may lead to degeneration of teeth supporting tissues with subsequent teeth loss. It is multifactorial inflammatory disease with genetic predisposition. Chronic inflammation in the periodontal tissue may be caused by multiply microorganisms (mainly Gram-negative anaerobic bacteria, "keystone pathogen" *Porphyromonas gingivalis*, Archaea, viruses) from the biofilm ("infectious inflammation") and non-infectious phlogogens ("sterile inflammation"). Predisposing factors also include vitamin C deficiency (scurvy), ionizing irradiation exposure, chemotherapeutic agents or cytostatic drugs, diabetes mellitus, smoking, ill-fitting dental appliances, etc.

The sulcular and junctional epithelia express different Pathogen Recognition Receptors, PRRs). After recognition of pathogen associated molecular patterns (PAMPs) and/or damage associated molecular patterns (DAMPs) acute inflammation starts with synthesis of proinflammatory cytokines, adhesion molecules and chemoattractants (Fig. 4-1).

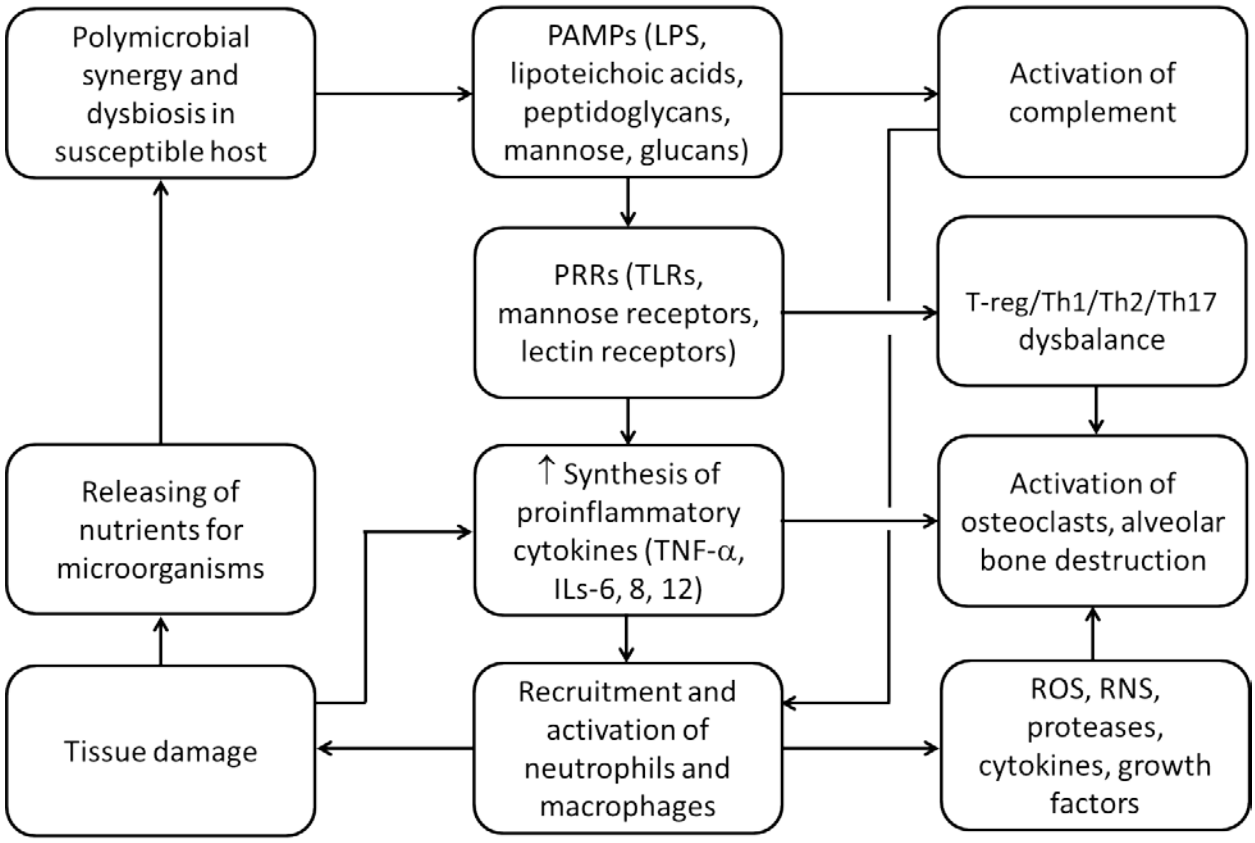


Figure 4-1. Simplified view of pathogenesis of chronic gingivitis

LPS, lipopolysaccharide; PAMPs, Pathogen Associated Molecular Patterns; PRRs, Pathogen Recognition Receptors; RNS, Reactive Nitrogen Species; ROS, Reactive Oxygen Species; TLRs, Toll-like receptors

Neutropenia, agranulocytosis, deficiency of leukocytes adhesion and their poor chemotaxis, activation and phagocytosis associate with most severe periodontitis. Substances which are released from activated neutrophils cause secondary injury thus perpetuating inflammatory process. Pathologic process starts as a chronic marginal gingivitis with formation of microbial biofilms around the teeth. The gingival sulcus is an excellent site for deposition of food debris and bacterial overgrowth resulting in the formation of periodontal pocket with purulent exudate in it. Destruction of collagen and epithelial hyperplasia, which are caused by activated matrix metalloproteinases, are seen in such periodontal pocket. Progressive resorption of alveolar bone by activated osteoclasts leads to loss of teeth.

It is important to note, that chronic periodontitis has not only local, but systemic effects due to development of systemic low grade inflammation (See in the Textbook "General pathophysiology: the essentials") which is proved by elevated concentrations of CRP and IL-6. This means that individuals suffering from chronic gingivitis have an increased rate of atherogenesis and higher incidence of cardiovascular complications. Moreover, periodontitis has been linked to diabetes, adverse pregnancy outcomes, rheumatoid arthritis, gastrointestinal diseases and oral cancer.

Pathophysiologic basis for the management of periodontitis: (1) physical removal of the plaque by scaling; (2) local or systemic antibacterial drugs; (3) periodontal surgery; (4) photodynamic therapy; (5) immunization against *P. gingivalis*; (6) novel approaches – drugs blocking C3 component of complement.

Disorders of salivary glands

The salivary glands are major (paired parotid, submandibular and sublingual glands) and minor which are widely distributed in the oral mucosa. They produce saliva which is necessary for food lubrication, swallowing, taste sensing, speech, food digestion (fermentation of carbohydrates with amylase), and innate immunity. Production of saliva is under control of autonomic nervous system: parasympathetic nerves enhance, whereas sympathetic nerves decrease salivary secretion. Causes of disorders of saliva production are listed in the Table 4-2.

Table 4-2. Salivary glands hypo- and hyperfunction

Types	Definition	Etiology	Consequences
Sialorhea (ptyalism)	Increased flow of saliva	Physiologic – teething, pregnancy; Pathologic – mental retardation, stomatitis, neurological disturbances, psychiatric disorders, gastric hypersecre-	Irritation of soft perioral tissues, dehydration in severe cases, neutralization of gastric juice and malabsorption

		tionm sialosis – symmetric painless hypertrophy of salivary glands	
Xerostomia	Decreased flow of saliva	Sjögren syndrome, sarcoidosis, mumps parotitis, Mikulicz's syndrome, megaloblastic anemia, dehydration or drug-induced – antihistamines, antihypertensives, antidepressants	Impaired swallowing, speech and food digestion, loss of protective properties of saliva with increased risk of caries and inflammatory diseases of oral cavity

Other common diseases of salivary glands include sialodenitis, benign and malignant tumors.

Selected diseases of the esophagus

Achalasia ("failure to relax" from Greek) is the most common motor disorder of the esophagus. It is characterized by failure of incomplete relaxation of the lower esophageal sphincter (LES) due to degeneration of the nerves in the Auerbach's plexus with degeneration of vagus and degeneration of neurons in the swallowing center. Significant role in such degeneration plays hereditary deficiency of neuronal NO-synthase in the nerves in the wall of the esophagus and lack of vasointestinal polypeptide (VIP), which stimulates nNOS activity. Lack of NO production leads to increased intracellular Ca^{2+} in esophageal muscular cells and their contraction. The consequences are an increase in LES pressure and increase in intraesophageal pressure with dysphagia (impaired swallowing) for liquids and solids. Proximal dilation of the esophagus results in the chest pain and regurgitation. Food fermentation in the lumen of the esophagus causes accumulation of lactate in it and heartburn.

Pathophysiologic basis for the treatment of achalasia: (1) nitrates and calcium channels blockers decrease tone of the LES; (2) endoscopic injection of botulinum toxin in the LES; (3) pneumatic dilation of the esophagus; (4) surgical myotomy.

Gastroesophageal reflux disease (GERD) is one of the commonest diseases with heartburn in developed countries. Gastroesophageal reflux is a normal physiologic phenomenon characterized by movement of gastric contents from the stomach to the esophagus. Aim of gastroesophageal reflux is to move out swallowed air from the esophagus. The following conditions making the reflex beneficial:

- Lower esophageal sphincter must have normal length (3-4 cm) and pressure (10-30 mm Hg) and normal number of episodes of transient relaxation (20-30 per hour).
- Diaphragmic crura must acts as an extrinsic sphincter of esophagus.
- Esophageal clearance (both peristalsis and saliva) must be able to neutralize the acid refluxed through lower esophageal sphincter.
- Stomach must empty properly.

When one or more from these conditions is impaired, gastroesophageal reflux becomes pathologic. GERD is characterized by frequent (more than 50 per hour) episodes of the LES relaxations with regurgitation of gastric acidic content in the esophagus, and damage of esophageal mucosa. Etiology, pathogenesis and complications of GERD are presented in the Fig. 4-2.

Most common complications of GERD are peptic stricture of the esophagus and Barrett's esophagus. The latter may be result of not only gastroesophageal reflux, but also duodenogastral reflux with regurgitation of duodenal content with bile in the esophagus. Barrett's esophagus is a result of the replacement of normal stratified, squamous epithelium to a polarized, columnar-lined epithelium with intestinal-type differentiation (Fig. 4-3). This condition is associated with 0.5-1% conversion rate to esophageal adenocarcinoma.

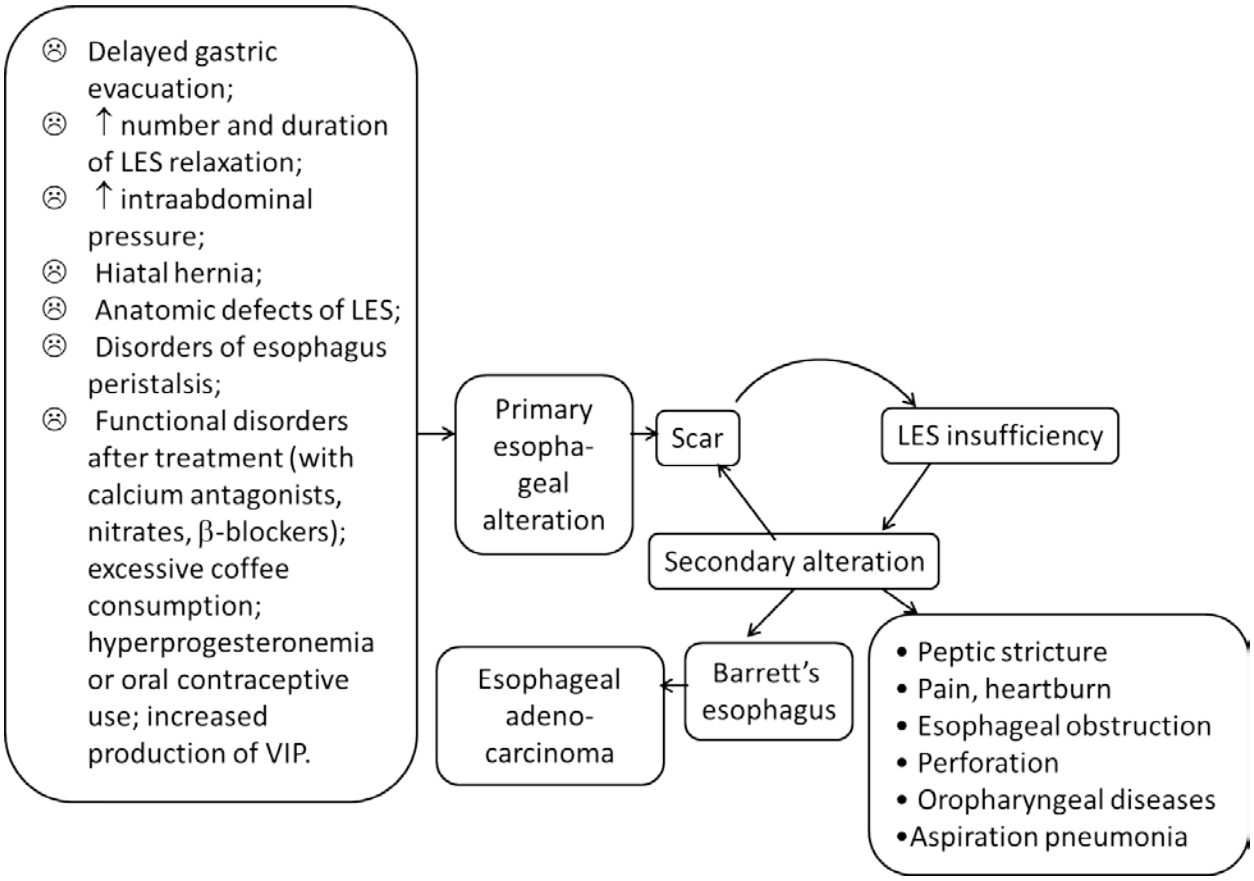


Figure 4-2. Pathogenesis of gastroesophageal reflux disease

Pathophysiologic basis for the treatment of gastroesophageal reflux disease: (1) lifestyle modifications – elevate the head of the bed, stop smoking and alcohol consumption, diet, reduce meal size, correction of obesity, avoid substances relaxing LES (See Fig. 4-2); (2) antacids; (3) acid-suppressing drugs (proton pump inhibitors, H_2-receptors antagonists; (4) antireflux surgery (fundoplication); (5) endoscopic antireflux procedures (for instance, thermocoagulation of the LES); (6) management of complications.

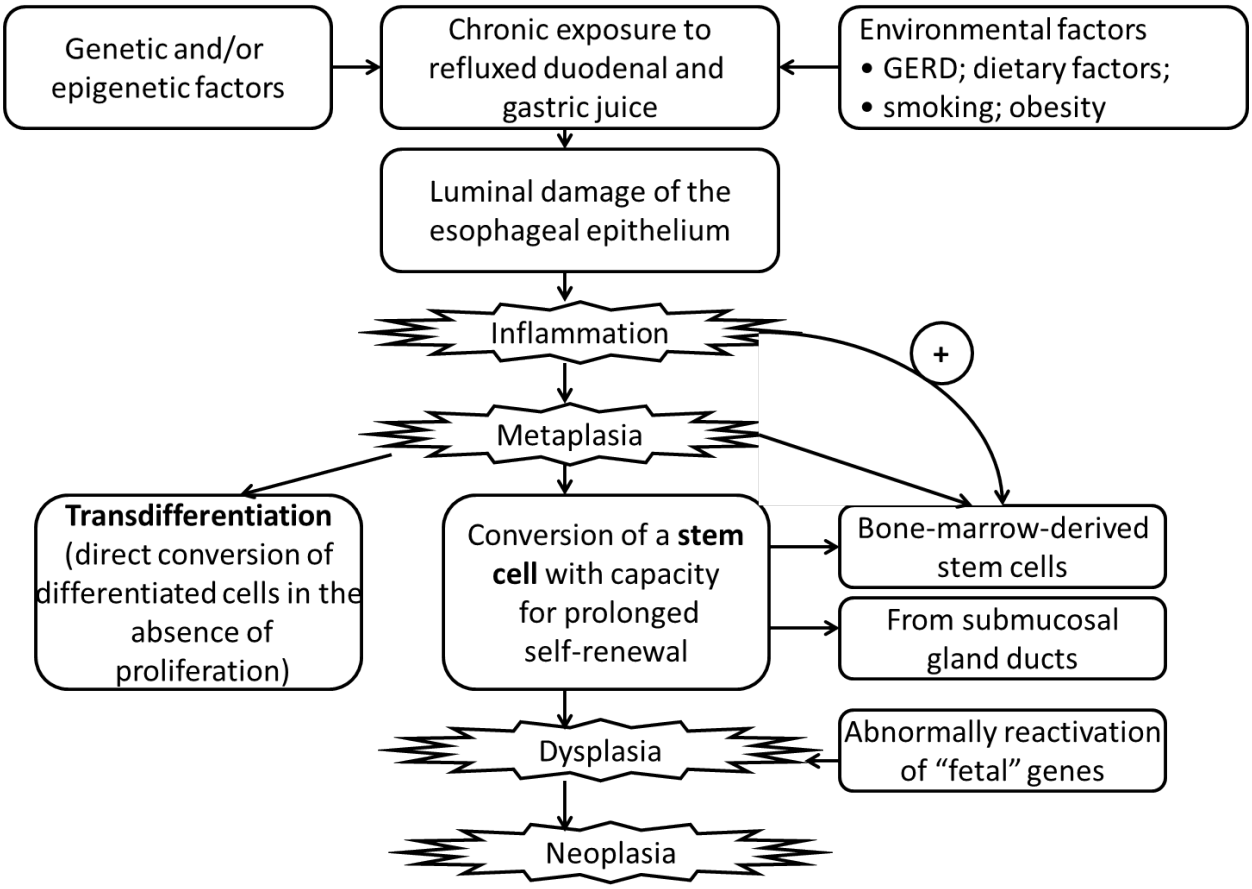


Figure 4-3. Mechanisms of metaplasia in Barrett's esophagus

Disorders of gastric secretion and motility

Dairy volume of gastric juice is approximately 1.5 l/day. Normal pH of gastric juice varies from 1 to 3.5. Main normal components of gastric juice are summarized in the Table 4-3. Small quantities of gastric lipase, gastric amylase and gelatinase are also produced in the stomach, but they seem to play only a minor role in the digestion of their substrates. Ghrelin is also produced in the stomach.

Table 4-3. Characteristic of gastric juice

Characteristic	Origin	Function
Hydrochloric acid HCl	Parietal cells	Important component of innate immunity; creates acidic milieu of the gastric juice thus activating pepsin and facilitating digestion of proteins in the stomach cells; regulation of epithelial cells' proliferation
Pepsin	Produced as a precursor pepsinogen by chief cells	Hydrolysis of 10-20% of proteins in the meal, especially hydrolyzes collagen – an important component of connective tissue of meats
Mucus	Mucous cells	Lubrication of gastric mucosa for food transport; protection from damage of gastric

		epithelial cells
Bicarbonates	Mucous cells	Protection of epithelial cells from aggressive action of the hydrochloric acid
Intrinsic factor	Parietal cells	Binding with vitamin B_{12} and its protection from premature destruction in the stomach

Secretion of gastric juice at rest is called basal secretion, whereas during and after meal gastric secretion will be raised – stimulated secretion. Stimulated secretion is a phasic process, developing through three stages: (1) cephalic phase; (2) gastric phase, and (3) intestine phase. Nerve stimulation of HCl secretion may be triggered by signals from limbic system or from stomach itself (caused by its distension, tactile stimulation of gastric mucosa, or by food-derived peptides or amino acids). Schematically simplified scheme of regulation of humoral-mediated HCl secretion by proton pump (H^+/K^+ ATPase) in parietal cells is presented in the Fig. 4-4. Other humoral factors are able to regulate gastric secretion: to stimulate – cholecystokinin, ACTH, growth hormone, glucocorticoids, thyroid hormones, parathormone, and insulin; to inhibit – gastric inhibitory peptide, produced in the duodenal mucosa, secretin, glucagon, vasointestinal peptide (VIP), kallikrein and epidermal growth factor. This knowledge helps us to explain causes of gastric secretion disorders.

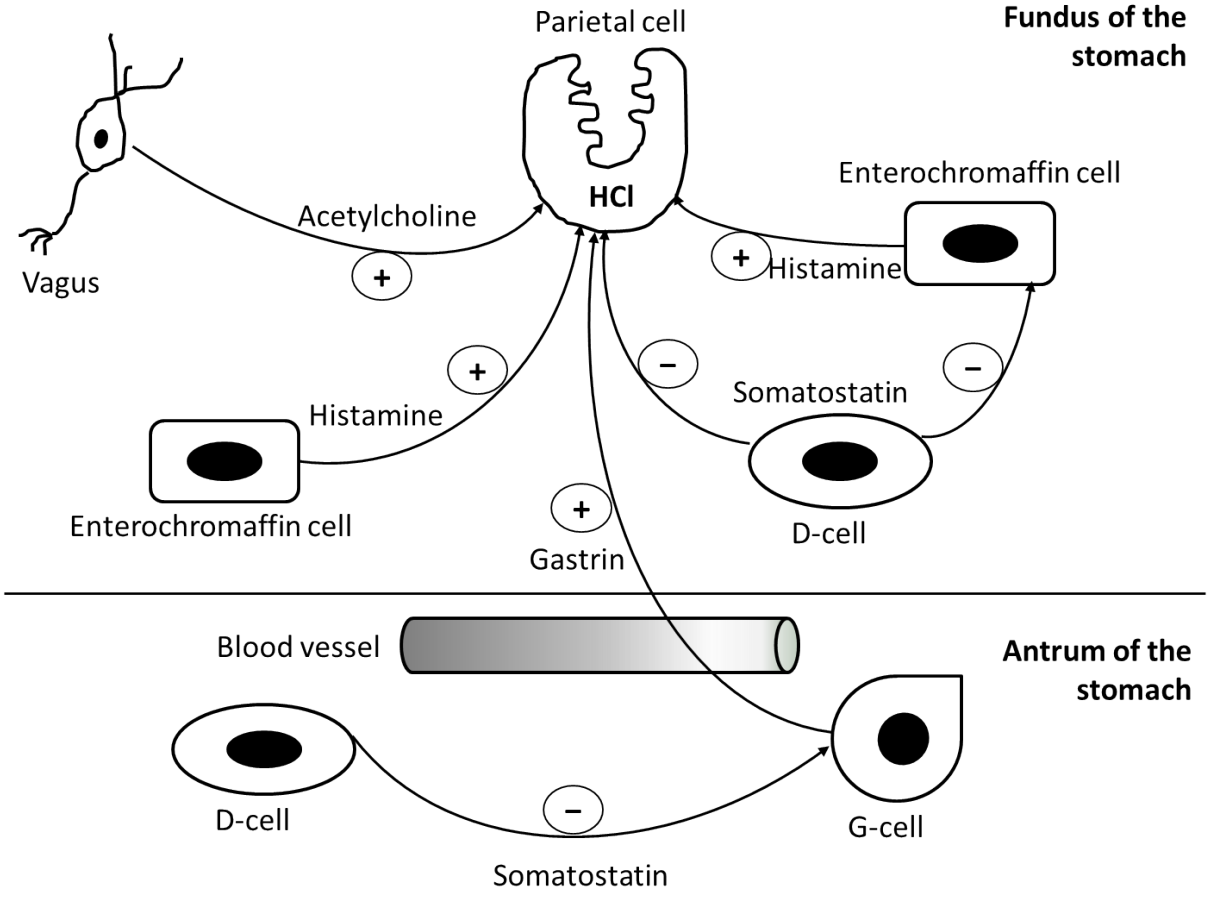


Figure 4-4. Regulation of gastric secretion

Gastric juice hypersecretion is characterized by production of increased amount of gastric juice and hyperproduction of hydrochloric acid (hyperchlorhydria). Basal and stimulated (after injection of histamine or pentagastrine) gastric secretion are elevated. Gastric juice hypersecretion may be caused by different causes, both functional and morphological. They include hypothermia, hot food, alcohol, constitutional vagotonia, psychoemotional disturbances, distension of antral part of the stomach, hyperplasia of parietal cells, hypergastrinemia due to gastrinoma – hormone-secreting pancreatic tumor originating from G-cells (Zollinger-Ellison syndrome), increased number of enterochromaffin cells in patients with carcinoid syndrome, systemic mastocytosis with histamine hyperproduction, some drugs (NSAIDs, glucocorticoids, insulin, etc.). Gastric juice hypersecretion may lead to peptic ulcer (See later), disorders of gastric motility (increase in gastric peristalsis) and food digestion.

Gastric juice hyposecretion usually combines with hypoacidity. Complete absence of free hydrochloric acid in the gastric juice is termed as achlorhydria. Loss of ability of gastric mucosa to secrete hydrochloric acid and enzymes is called by achylia. In such condition basal and stimulated secretion of hydrochloric acid is significantly depleted. Main causes of gastric juice hyposecretion are atrophic or autoimmune gastritis, gastric cancer, surgical rejection of the stomach or its parts, or drug-induced suppression of gastric secretion (anticholinergic drugs, antagonists of H_2-receptors, proton pump inhibitors), somatostatin-producing tumors. Hyposecretion associates with poor food digestion and nutrients absorption (See later "Malabsorption syndrome"), delayed gastric motility, loss of antibacterial effect of gastric juice, increased risk of infections, atrophy of gastric mucosa, especially combined with Helicobacter Pylori infection, disorders of iron, calcium, and vitamin B_{12} absorption.

Disorders of the stomach motility include hypermotility, hypomotility, and vomiting (Table 4-4).

Table 4-4. Pathophysiologic characteristic of gastric motility disorders

Type of motility disorder	Causes	Consequences
Hypermotility	• Abnormal nutrition: coarse food, alcohol; • Emotional disorders: anxiety, anger; • Drug-induced: cholinergic drugs, histamine; • Somatic diseases: gastritis, peptic ulcer, nephrolithiasis, gall stone disease, gastric hypersecretion	Pain, malabsorption
Hypomotility	• Increased production of gastric inhibitory peptide, VIP, secretin, catecholamines; • Activation of the sympathetic nerves,	Pain, malabsorption, sensation of gastric distension, eructation,

	• Somatic diseases: gastritis, splanchnoptosis, loss of weight, vagotomia, abdominal surgery	nausea, vomiting

Vomiting starts with hypersalivation and the sensation of nausea. Reverse peristalsis empties content from the proximal part of the small intestine into the stomach. The glottis closes, preventing aspiration of vomitus into the trachea. The breath is held in mid inspiration. The muscles of the abdominal wall contract, and because the chest is held in a fixed position, the contraction increases intra-abdominal pressure. The lower esophageal sphincter and the esophagus relax, and the gastric contents are ejected. Etiology and pathogenesis of vomiting are illustrated in the Fig. 4-5.

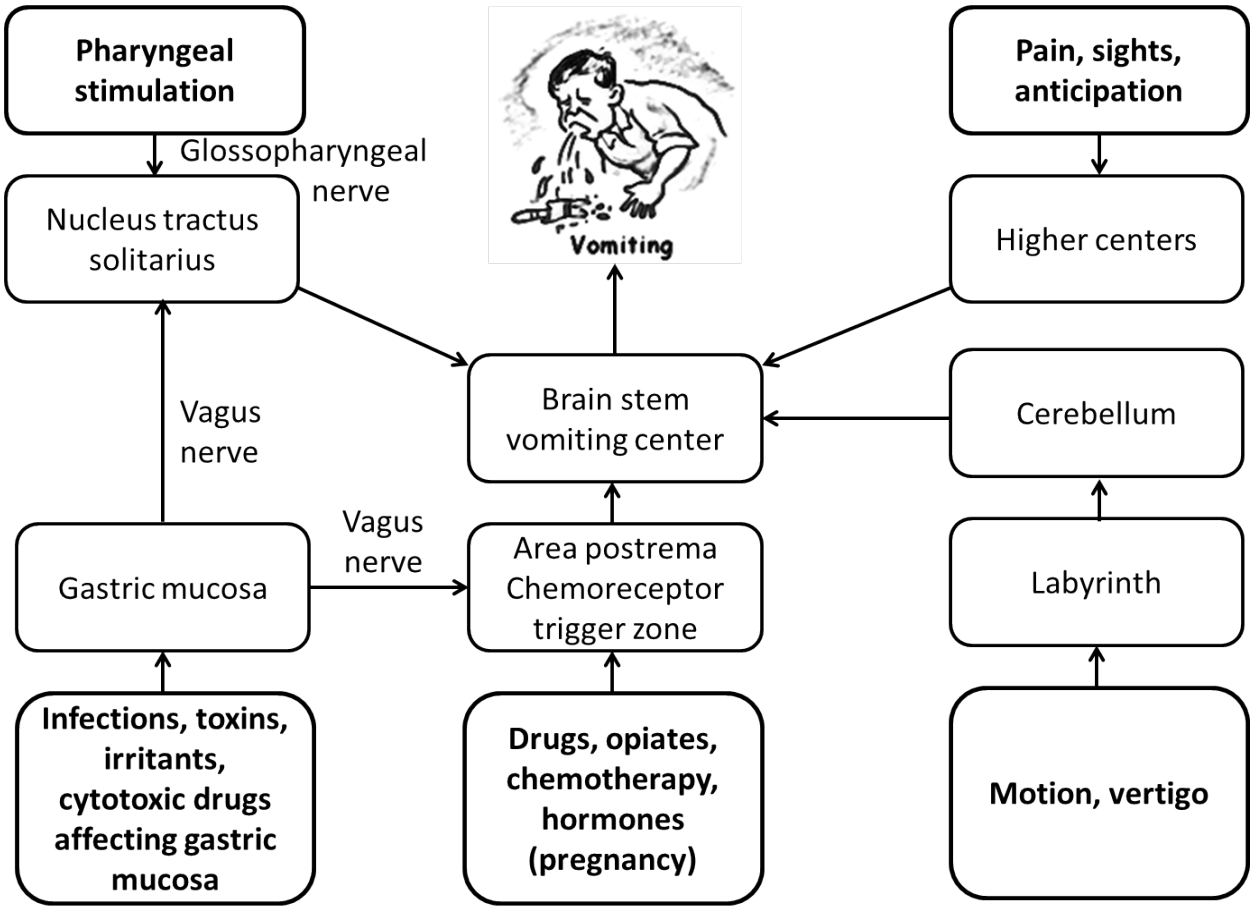


Figure 4-5. Causes and mechanisms of vomiting

Serotonin released from enterochromaffin cells in the small intestine initiates impulses via 5-HT_3 receptors that trigger vomiting. In addition, there are dopamine D2 receptors and 5-HT_3 receptors in the area postrema and adjacent nucleus of the solitary tract. 5-HT_3 antagonists such as ondansetron and D_2 antagonists such as chlorpromazine and haloperidol are effective antiemetic agents. Corticosteroids, cannabinoids, and benzodiazepines are also useful in treatment of the repeated vomiting produced by chemotherapy.

Single vomiting has protective significance, as a rule; because of it helps to remove pathogens from the organism. Chronic, repeated vomiting may lead to deleterious consequences:

- Malnutrition;
- Hypovolemia with dehydration in infants with subsequent release of ADH and aldosterone;
- Metabolic alkalosis due to loss of H^+;
- Electrolyte disorders (hyponatremia or hypernatremia, hypokalemia);
- Gastric rupture;
- Tears in the esophageal wall with arterial esophageal bleeding (Mallory-Weiss syndrome);
- Dental caries caused by hydrochloric acid exposure on the dental enamel;
- Inflammation of the oral mucosa;
- Aspiration pneumonia.

Gastritis and peptic ulcer

Gastritis is an inflammation of the stomach proved by gastroscopy. It can be classified into acute and chronic. Peptic ulcer is a multifactorial disease affecting mucosa, submucosal, sometimes even muscular and serosal layers of the esophagus as a complication of gastroesophageal reflux disease, stomach and duodenum. It is an acid-dependent disorder. At least 10% of population have or will have peptic ulcer. Pathogenesis of peptic ulcer and gastritis can be simplified as a disbalance between protective and aggressive factors (Fig. 4-6) as a result (1) predomination of aggressive factors; (2) insufficiency of protective factors; (3) combination (1) and (2).

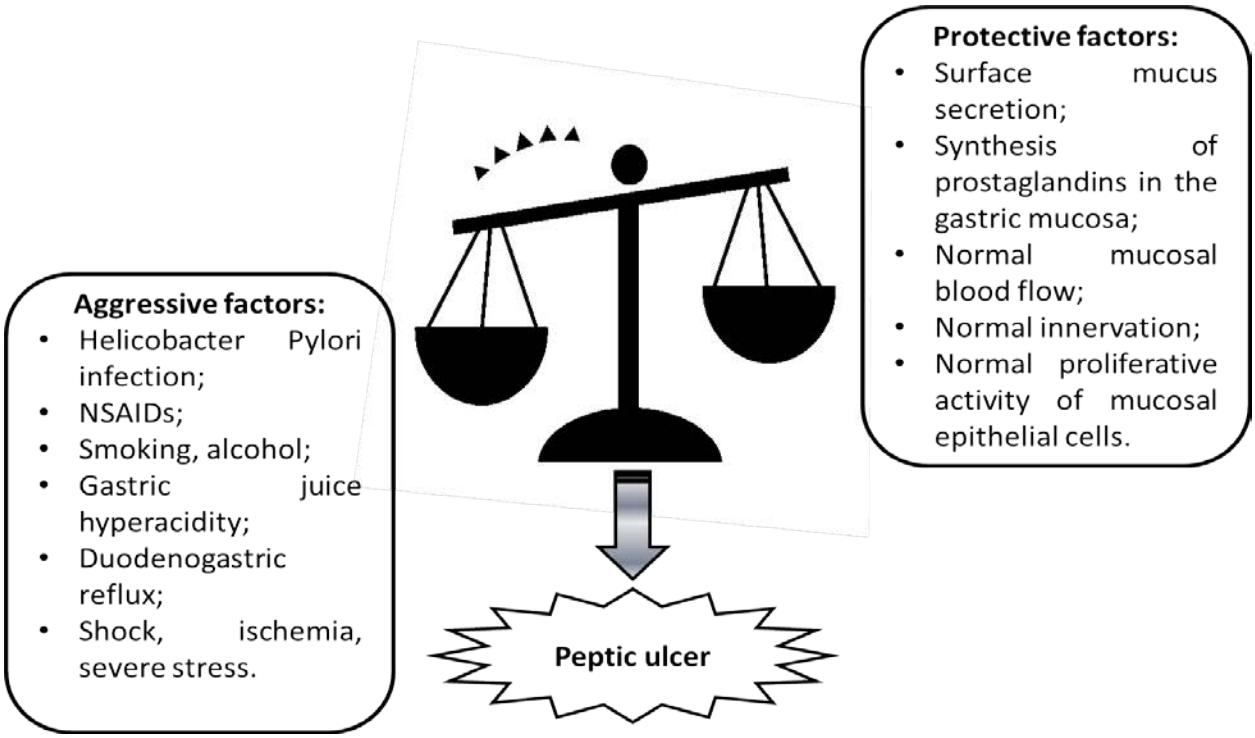


Figure 4-6. Pathogenesis of peptic ulcers affecting stomach or duodenum

Most common causes of peptic ulcers are presented below:

- Helicobacter Pylori infection
- NSAIDs
- Stress ulcer

Uncommon specific forms of peptic ulcer are derived from:

- Hydrochloric acid hypersecretion (in patients with gastrinoma or Zollinger-Ellison syndrome – tumor derived from cells in the duodenum, pancreas or peripancreatic soft tissues producing gastrin, which stimulated HCl secretion; mastocytosis - inherited or sporadic; basophilic leukemias; antral G-cell hyperfunction/hyperplasia);
- Viral infections (caused by Herpes simplex virus, cytomegalovirus)
- Other cases including duodenal obstruction; vascular insufficiency; radiation-induced and/or chemotherapy-induced peptic ulcer; rare genetic subtypes; amyloidosis type III; tremor-ulcer-nistagmus syndrome.

Acute gastritis is commonly caused by NSAIDs, alcohol, smoking, chemotherapy, uremia, systemic infections, severe stress, ischemia, shock, and exposure of acids or alkali on the gastric mucosa, bile reflux causing detergent action on the gastric mucosa, and mechanical trauma during nasogastral aspiration. Chronic gastritis may be autoimmune or related to H. Pylori infection (See Part XIV in the Textbook "General pathophysiology: the essentials").

Role of H. Pylori in the pathogenesis of gastrointestinal diseases. H. Pylori is small, S-shaped, gram-negative urease-producing bacteria, which colonizes mucus-secreting epithelial cells of the stomach and duodenum with oral pathway of transmission. The prevalence of H. Pylori infection among middle-aged adults is over 80% in many developing countries; as compared with 20-50% in industrialized countries. Infection caused by H. Pylori is an example of an infectious process, which depends on both particular features of micro- and macroorganism. Not more than 10-20% of individuals infected with these bacteria will develop peptic ulcer. Main factors of H. Pylori pathogenicity are urease, which degrading urea and neutralize HCl with production of toxic ammonia chloride; flagella which are responsible for motility; proteins adhesins (Bab A) mediating attachment of microorganism to gastric epithelial cells and secreted exotoxins.

Vac A or vacuolating cytotoxin causes series of harmful effects: (1) pore formation in the gastric epithelial cells and epithelial cells damage; (2) formation of vacuoles in the mucosal epithelial cells and damage of their cytoskeleton; (3) impairment of gap junctions between adjacent mucosal epithelial cells facilitating spreading of the H. Pylori in the submucosal layers of the stomach; (4) increase in vascular permeability; (5) releasing of cytochrome c from mitochondria of mucosal epithelial cells thus triggering intrinsic pathway of their apoptosis; (6) impairment of normal proliferation and differentiation of mucosal epithelial cells; (7) suppression of immune response via impairment of phagosomes formation, poor presentation of antigens of H. Pylori to T-cells, and suppression of Th1-mediated immune

reactions thus creating favorable conditions for the development of chronic inflammation in the gastric mucosa.

Most pathogenic strains of H. Pylori have in their genome "cag A island" encoding the same protein Cag A. It is "injected" in gastric mucosal epithelial cells, phosphorylates tyrosine kinase and activates kinase cascade, which results in the synthesis of proinflammatory cytokines, impairment of proliferation and apoptosis of mucosal epithelial cells with subsequent metaplasia of epithelial cells. Presence of "cag A island" and secretion of protein Cag A associates with increased risk of peptic ulcer and gastric adenocarcinoma.

Pathogenesis of inflammation in the gastric mucosa caused by H. Pylori.

Acute inflammation develops following several days or weeks after contamination with H. Pylori: presentation of H. Pylori antigens with MHC-II molecules → triggering of "infectious" inflammation → activation of transcription factors NF-kB and AP-1 in the gastric epithelial cells → synthesis of proinflammatory cytokines including IL-8, neutrophils activating peptide, and Growth Related Oncogen-α (GRO-α) → recruitment of neutrophils in the site of inflammation under influence of exogenous and endogenous chemoaatractants → releasing of ROS, RNS and proteases from activated neutrophils → secondary oxygen-dependent and oxygen-independent damage of mucosal epithelial cells → development of antral gastritis. Antral gastritis associates with hypersecretion of hydrochloric acid because of:

- Proinflammatory cytokines TNF-α, IL-1 and IFN-γ stimulates G-cells to produce gastrin (See Fig. 4-4). Gastrin stimulates ECLs producing histamine, which interacts with H_2-receptors on the surface of parietal cells and activates them. Parietal cells which are unaffected in antral gastritis produce more HCl. Continuous hyperchlorhydria shifts balance between protective and aggressive factors (See Fig. 4-6) and provokes development of duodenal ulcer.
- H. Pylori suppresses activity of somatostatin-secreting D-cells, which normally inhibit activity of G-cells (See Fig. 4-4) thus supporting hyperchlorhydria.

Chronic inflammation caused by H. Pylori may last several weeks, months and even years. A lot of lymphocytes present in the site of inflammation. Their extravasation is required adhesion molecules ICAM-1 and VCAM-1. Macrophages also play an important role in the development of chronic inflammation. They secrete IL-8 and IL-12, which polarize immune response towards Th1. Th1 release IFN-γ. It stimulates expression of MHC-II and ligands B7-1 and B7-2 on the surface of gastric epithelial cells, which may be damaged by autoreactive T-cells. Expression of Fas-L on the surface of mucosal epithelial cells is stimulated, so epithelial cells die from exogenous-triggering pathway of apoptosis. Cytotoxin Vac A, damage of mucus-derived glycoproteins by activated phospholipase A_2 and apoptosis of mucosal epithelial cells result in the loss of protective barrier of gastric mucosa. Activation of macrophages and production of proinflammatory substances facilitate damage of gastric mucosa and subsequent spreading of H. Pylori. During

initial stages of disease gastric secretion may increase, during late stages it usually decreases. Pangastritis associates with hyposecretion of hydrochloric acid which is resulted from:

- Suppression of histamine production by ECLs caused by direct action of H. Pylori;
- Direct damage of parietal cells by H. Pylori;
- Formation of autoantibodies against H^+/K^+-ATPase in parietal cells.

In turn, hypersecretion of HCl stimulates hyperproduction of gastrin. Hypergastrinemia stimulates proliferation of gastric mucosal epithelial cells. Such abnormalities in conditions of chronic inflammation and persistence of H. Pylori impair cell cycle of epithelial cells, leads to decrease in amounts of glands in the gastric mucosa which is followed with atrophy and sometimes – with **gastric adenocarcinoma**. H. Pylori is an obligatory carcinogen. Chain of events leading to gastric adenocarcinoma can be presented as following: infection with H. Pylori → superficial gastritis → atrophic gastritis → intestinal type of metaplasia of epithelial cells → dysplasia of epithelial cells → gastric adenocarcinoma. To better understand links between chronic inflammation and cancer and to evaluate role of H. Pylori in the carcinogenesis it is strongly recommended to revise Part XV "Pathophysiology of the tumor growth" in the Textbook "General pathophysiology: the essentials". Summarized natural history of H. Pylori infection is illustrated in the Fig. 4-7.

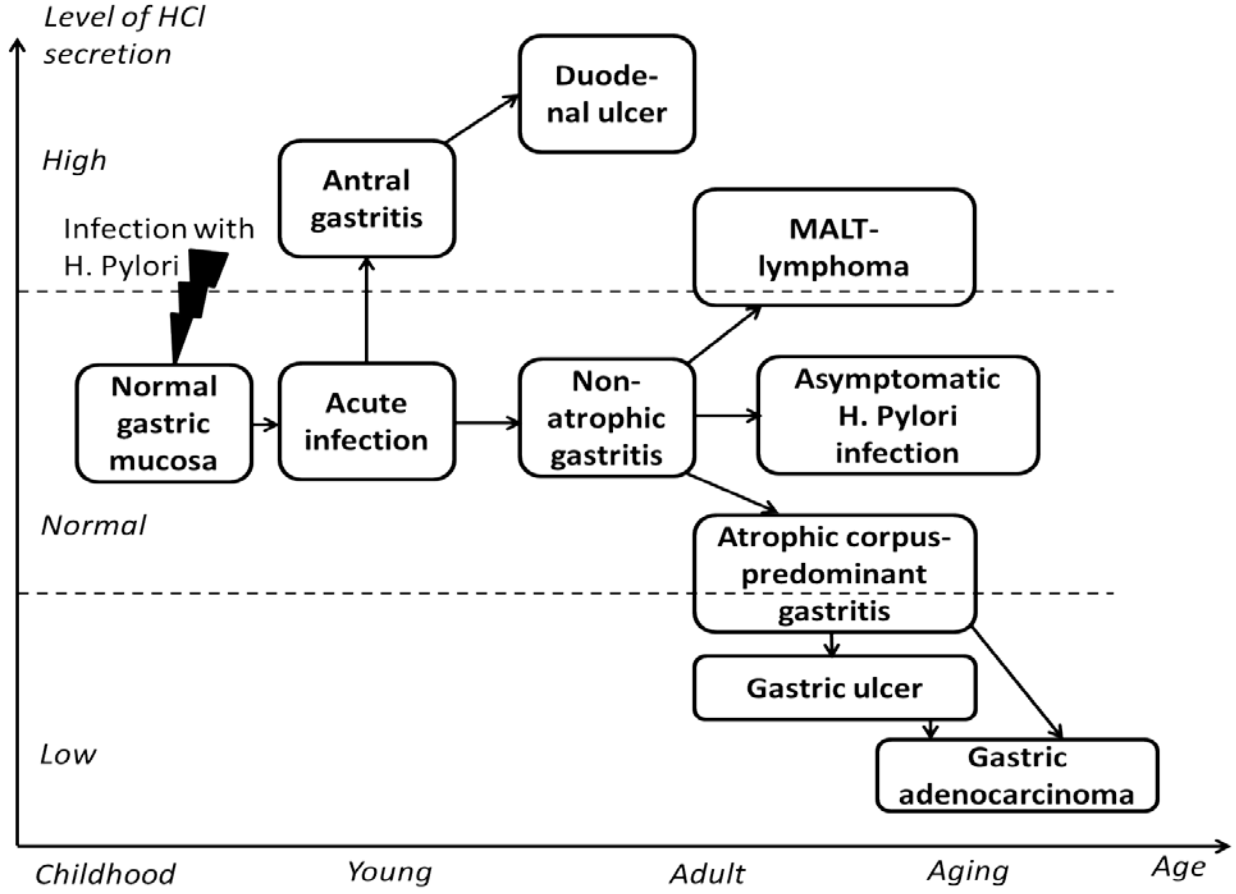


Figure 4-7. Natural history of H. Pylori infection

Mucosal Assosiated Lymphoid Tissue Lymphoma (**MALT-lymphoma**) may develop in some patients with non-atrophic gastritis caused by H. Pylori. Antigens of the microorganism are recognized by APCs. They present antigens to CD4+ T-cells with subsequent production of cytokines initiating proliferation of B-cells. Prolonged persistence of H. Pylori leads to mutations in the genome of B-cells, and mutated cloned of B-cells begin to produce Ig A, G, M. B-cells also may differentiate into plasma cells. MALT-lymphoma is a unique neoplasm, which may regress in 75% of patients after eradication of H. Pylori.

NSAIDs-associated gastropathy. Millions of people in the world regularly use NSAIDs to relieve pain, suppress inflammation and manage fever. NSAIDs cause adverse effects, such as anorexia, dyspepsia, abdominal pain, gastritis, erosions, gastric ulcer, and occult or gross gastrointestinal bleeding. To understand pathogenesis of such pathologies it is necessary to recall pathway of arachidonic acid metabolism (Fig. 4-8). Membrane lipids supply the substrate for the synthesis of eicosanoids and platelet-activating factor. Eicosanoids including prostaglandins (PGs); prostacyclin (PGI_2), thromboxane A_2 (TXA_2), leukotrienes (LTs), and lipoxins are arachidonate metabolites. COX-dependent and LOX-dependent pathway (the latter is not shown in the Fig. 4-8) contribute to the synthesis of eicosanoids. Several classes of drugs, most notably aspirin, the traditional COX-1 blocking NSAIDs, and the specific inhibitors of COX-2, such as the coxibs, owe their principal therapeutic effects to blockade of eicosanoid formation.

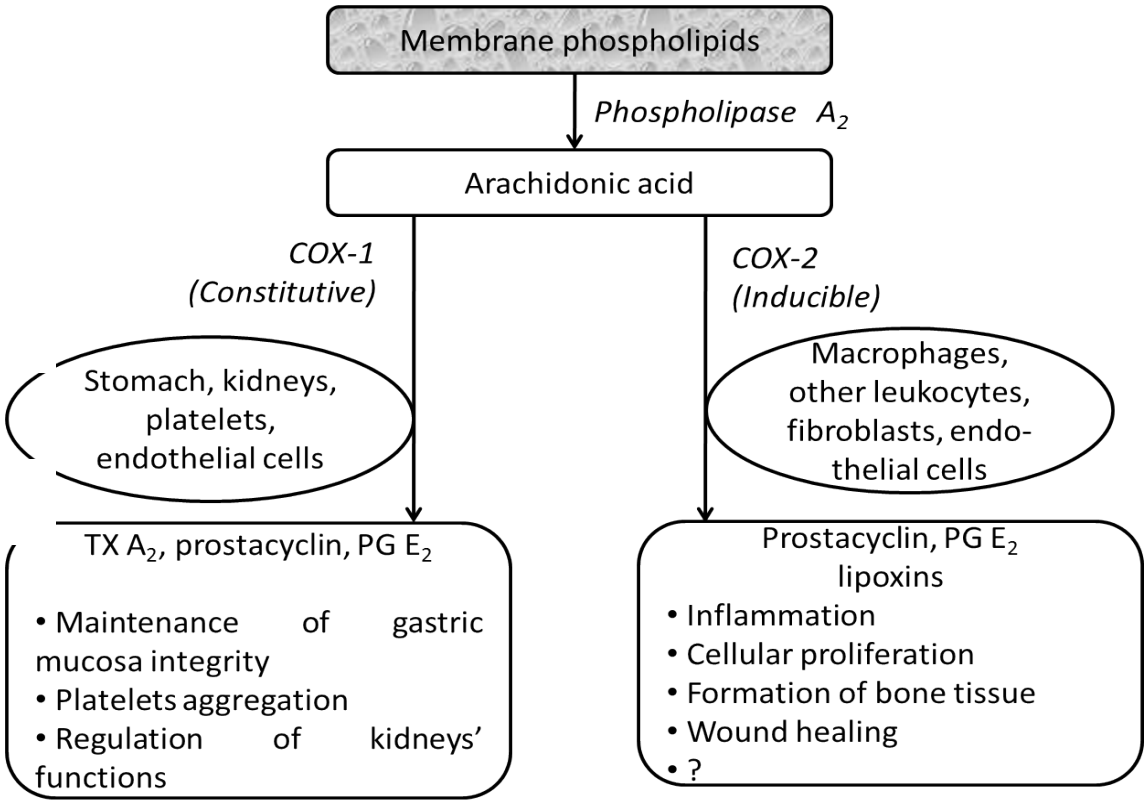


Figure 4-8. Simplified scheme of COX-dependent metabolism of the arachidonic acid

Pathogenesis of NSAIDs-associated gastropathy and therapeutic approaches to it prevention are presented in the Fig. 4-9.

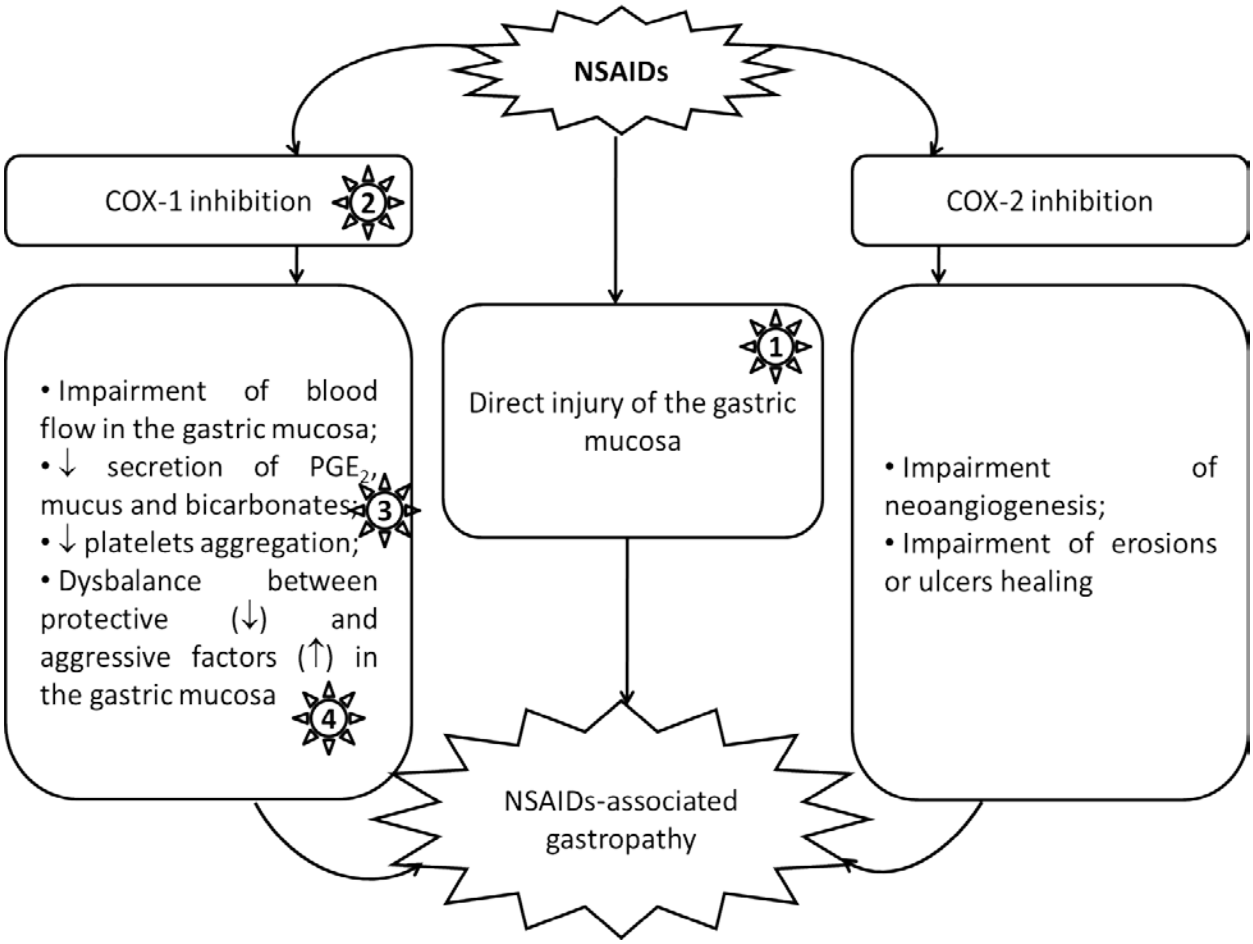


Figure 4-9. NSAIDs-associated gastropathy: pathogenesis and prevention

Numerals inside figures indicate approaches to the prevention and management of NSAIDS-associated gastropathy: 1 – recommendations to use oral NSAIDs after meal followed with drinking a sufficient amount of water or use NSAIDs with intestine-soluble coat; 2 – to use selective COX-2 inhibitors if it is possible; 3 – to use synthetic analogs of PgE_2 – misoprostol; 4 – to use antisecretory agents (H_2-receptors antagonists or proton pump inhibitors) and surface-active agents (sucralfate).

Stress-related ulcer. Endoscopies performed within 72 h of the onset of critical illness have revealed gastroduodenal lesions (erosions, submucosal hemorrhages or even gross bleeding) in 75–100% of all cases. Shunting of blood away from the viscera and skin (so-called centralization of blood flow) is an adaptation to hypoperfusion of tissues that allows maintaining perfusion to the vital organs (brain and heart) during an insult. Gastric mucosal perfusion decreases during critical illness owing to a number of factors: (1) activation of the sympathetic nervous system; (2) increased catecholamine release and vasoconstriction; (3) hypovolemia; (4) decreased cardiac output; (5) release of proinflammatory cytokines; (6) impaired production of vasodilator nitric oxide. As a consequence of splanchnic

hypoperfusion, gastrointestinal motility is decreased, delaying the removal of acidic material and other irritants from the stomach, prolonging exposure to gastric acid and resulting in a corresponding increase in the risk of ulceration (Fig. 4-10).

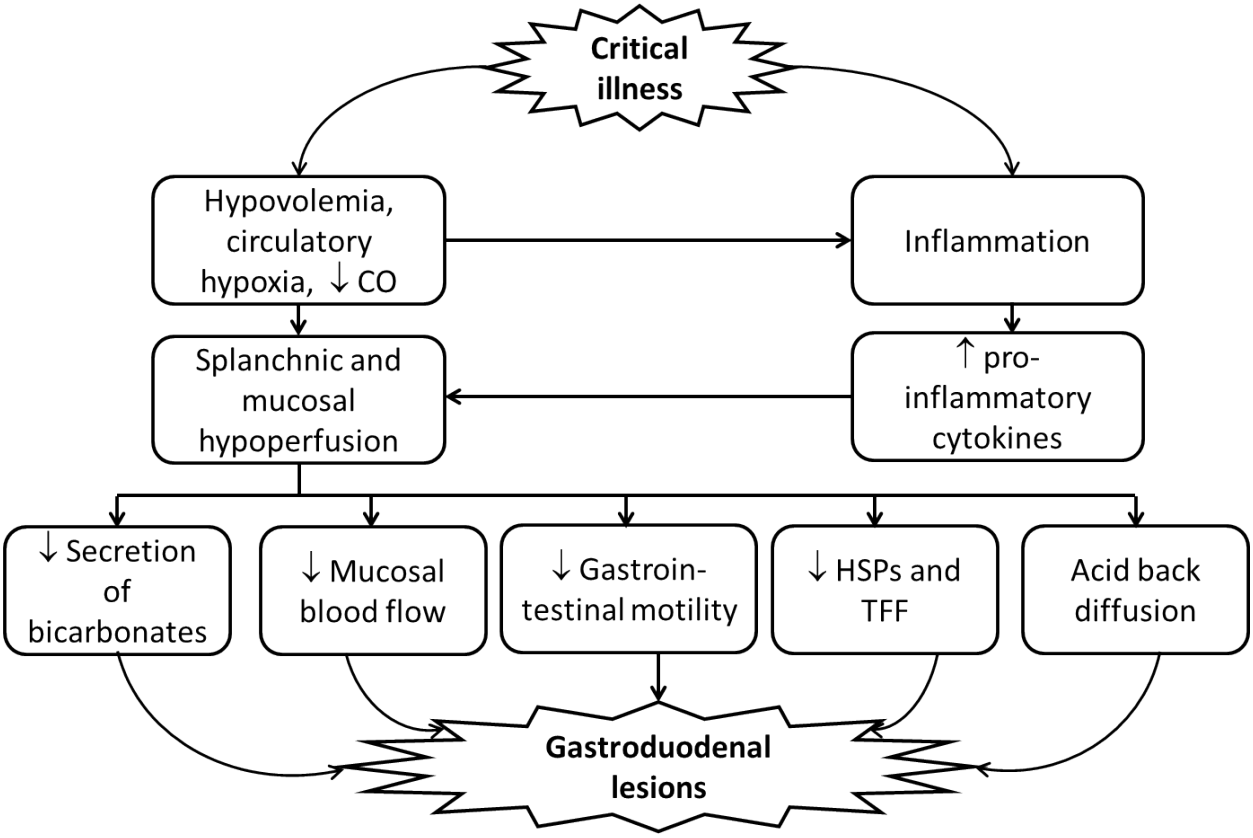


Figure 4-10. Pathogenesis of stress-related gastroduodenal lesions

CO, cardiac output; HSPs, heat-shock proteins; TTF, trefoil factor family peptides

Nowadays heat-shock proteins and trefoil factor family peptides are thought as new protective factors of gastroduodenal mucosal epithelial cells.

Peptic ulcer disease may lead to different, sometimes life-threatening complications:

- Gastrointestinal bleeding;
- Perforation;
- Obstruction;
- Malignant transformation.

Pathophysiologic basis for the treatment of peptic ulcer: (1) etiotropic treatment, for example, eradication of H. Pylori with antimicrobial therapy or prevention of NSAIDs-associated gastropathy; (2) antisecretory agents – H_2 receptors antagonists, proton pump inhibitors; (3) symptomatic therapy – antacids; (4) prevention and management of complications; (5) surgical therapy if drug therapy is ineffective.

Dumping syndrome

Dumping syndrome is a complication of gastric and esophageal surgery such as vagotomy with pyloroplasty, esophagectomy, Nissen fundoplication, and bariatric surgery. Symptoms of dumping syndrome can be classed as early, developing immediately after meal (abdominal pain, diarrhea, borborygmi, nausea, bloating, fatigue, a desire to lie down after meals, facial flushing, palpitations, perspiration, tachycardia, hypotension and syncope) or late, which occur 1-3 hours after meal including hypoglycemia, perspiration, palpitations, hunger, fatigue, confusion, aggression, tremor and syncope. Pathogenesis of dumping syndrome can be explained as a chain of events: gastric surgery → reduction of gastric volume → rapid passage of nutrients to the small intestine → arrival of hyperosmolar contents to the duodenum → moving of fluid from the intravascular component to the intestinal lumen → decrease in the volume of circulating fluid → tachycardia, syncope (Fig. 4-11).

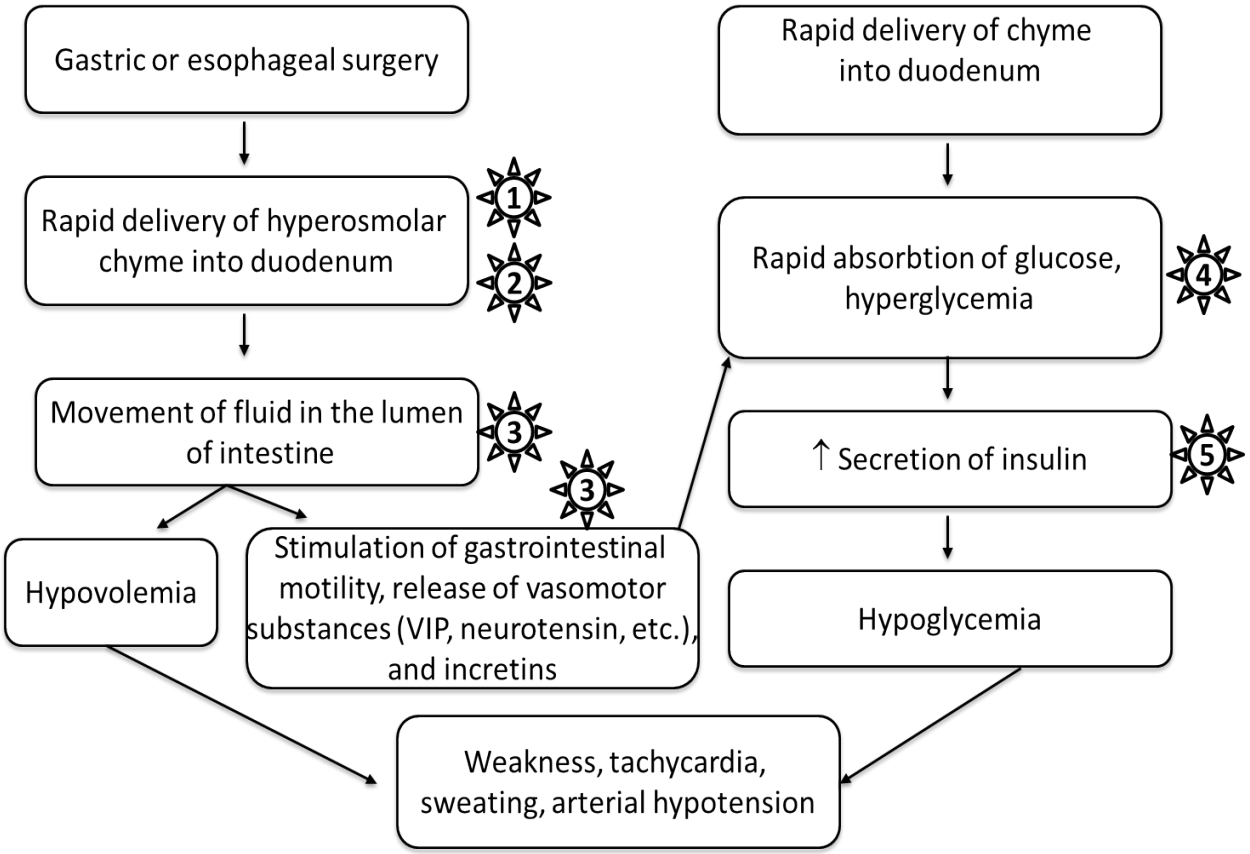


Figure 4-11. Pathogenesis of dumping syndrome

Numerals inside figures indicate approaches to the management of dumping syndrome: 1 – dietary measures (intermittent nutrition); 2 and 3 – somatostatin analogs (octreotide) which retard gastric emptying rate, retard transit through the small intestine, inhibit the release of gastrointestinal hormones, inhibit insulin secretion and inhibit postprandial vasodilation; 4 – acarbose (α-glycosidase hydrolase inhibitor) that inhibits the α-glycosidase-mediated production of monosaccharides from carbohydrates in the epithelial brush border cells of the small intestine; 5 – diazoxide, a potassium channel activator, which hyperpolarizes cells, including

pancreatic β-cells and inhibits voltage-sensitive calcium channels preventing insulin release. Insufficient results of above mentioned approaches may require surgery.

The fluid shift into the duodenum also causes duodenal distention with subsequent cramp-like contractions. Increased release of several gastrointestinal peptide hormones – enteroglucagon, peptide YY, pancreatic polypeptide, vasoactive intestinal polypeptide (VIP), glucagon-like peptide 1 and neurotensin affect not only gastrointestinal motility and secretion, but also cause hemodynamic effects including systemic hemoconcentration and hypotension as a result of splanchnic vasodilation. Late dumping symptoms are attributed to reactive hypoglycemia. Normally, the presence of glucose in the jejunum is a strong stimulus for insulin secretion. The rapid delivery of carbohydrates to the small intestine in dumping syndrome, therefore, causes excessive insulin secretion that subsequently results in hypoglycemia. It also is resulted from the action of glucagon-like peptide.

Malabsorption syndrome

Malabsorption syndrome (French prefix "mal-" means bad, poor) is a clinical syndrome which is resulted from poor absorption of nutrients in the intestine. It is due or to abnormal food digestion (maldigestion) or to abnormal absorption of nutrients proper. Different causes may lead to the malabsorption syndrome (Fig. 4-12):

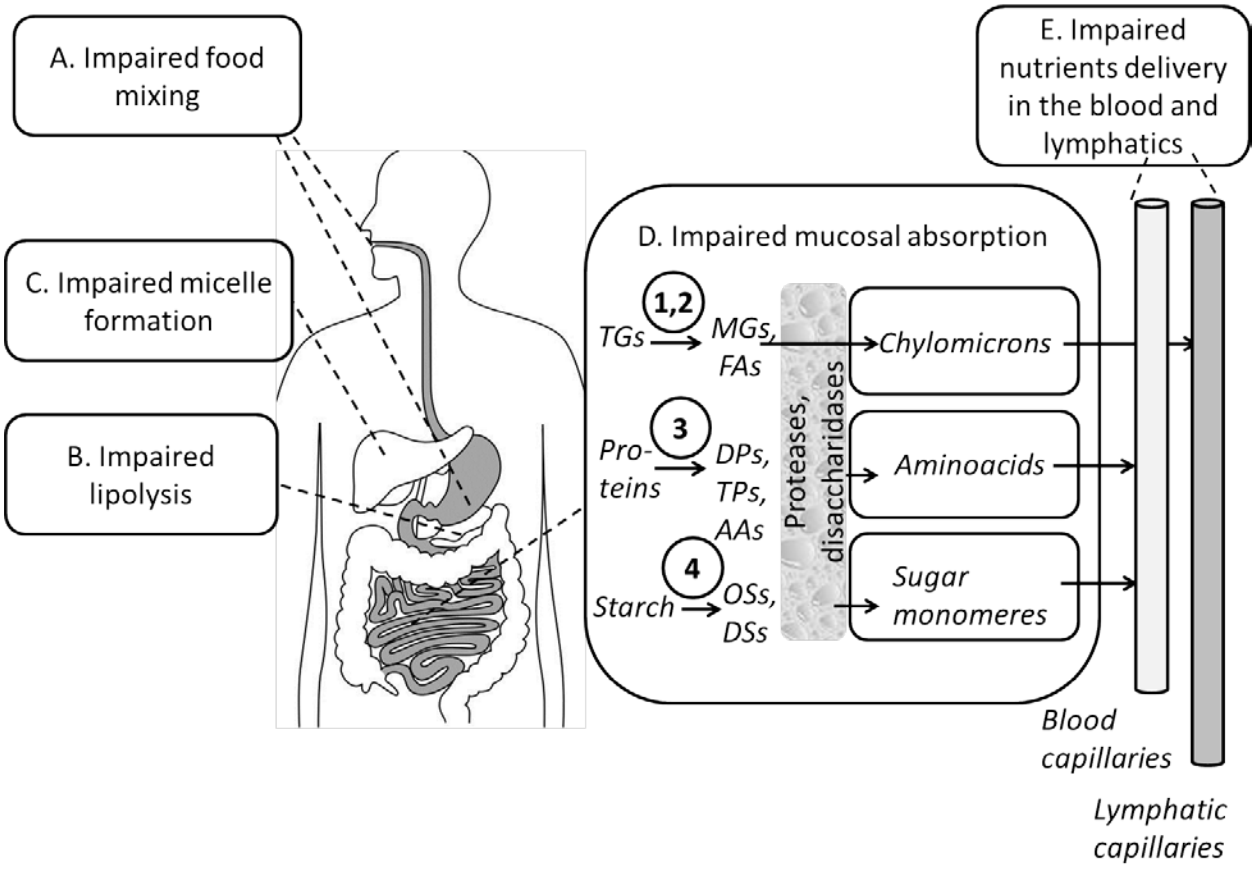


Figure 4-12. Basic mechanisms of malabsorption

AA, amino acids; DPs, dipeptides; DSs, disaccharides; FAs, fatty acids; MGs, monoglycerides; OSs, oligosaccharides; TGs, triglycerides; TPs, tripeptides; 1 – lipase, 2 – colipase, 3 – proteases, 4 – amylase.

A. Impaired food mixing may be resulted from poor chewing (in arthritis affecting mandibular joints, other diseases of oral cavity and teeth); from hyposalivation leading to the xerostomia (after injury of the salivary glands with ionizing irradiation or autoimmune process, or after use of anticholinergic drugs or some antidepressants). Alteration of the saliva composition also may cause malabsorption. Improper mechanical and chemical food processing in the oral cavity impairs further digestion in the stomach. Impaired food mixing also is commonly observed after partial or total gastrectomy or after gastric surgery bypass as well as in dumping syndrome.

B. Impaired lipolysis is a frequent cause of malabsorption, which is commonly due to exocrine pancreatic insufficiency. Normally, pancreas produces different digestive enzymes, and some of them in active forms, such as lipase, amylase, deoxyribonuclease, ribonuclease, or as proenzymes, such as trypsinogen, chymotrypsinogen, proelastase, procarboxypeptydase and phospholipase A_2. The latter are normally activated to the active enzymes in the duodenum. Hyposecretion of pancreatic enzymes is seen in chronic pancreatitis, pancreatic cancer and pancreatic fibrosis. Initial stages of pancreatic insufficiency are manifested by poor secretion of lipase and inadequate absorption of fats. Above-mentioned pathologies often coexist with lack of HCO_3^- secretion in the pancreatic juice with further inactivation of lipase, precipitation of bile acids and severe malabsorption of fats with clinical hallmark – clammy “fatty stools” with rank smell (steatorrhea). In advanced stages of exocrine pancreatic insufficiency synthesis of protein-digesting enzymes (trypsinogen, chymotrypsinogen, proelastase, procarboxypeptydase) diminishes, which leads to poor digestion of proteins and malabsorption of amino acids in the small intestine. Activity of amylase (destroying carbohydrates), decreases only slightly, that is why malabsorption of carbohydrates in exocrine pancreatic insufficiency is infrequent. Excessive secretion of gastric juice in patients with gastrinoma (Zollinger-Ellison syndrome) denaturates lipase thus leading to the malabsorbtion. Rare hereditary deficiency of the intestinal cofactor of lipase – colipase also may result in the malabsorption.

C. Impaired micelle formation may be found in liver diseases associated with impairment of the bile formation, and in obstruction of bile ducts with stones, tumors, helminthes or strictures. Lack of bile acids in the duodenum results in the poor emulsification of dietary fats and steatorrhea. Inadequate absorption of fat-soluble vitamins (A, D, E, K) manifests with clinical signs of hypovitaminosis (See Table 11-1 in the Textbook “General pathophysiol-

ogy: the essentials"). After deconjugation of fatty acids in the intestine by microbiota (its overgrowth may be due to slowing of the intestine peristalsis – in diabetic polyneuropathy, systemic diseases affecting connective tissue in the gastrointestinal tract, after abdominal surgery complicated with blind loop syndrome, in intestinal diverticulum) bile acids gain amphyphilic properties, stimulate secretory activity of enterocytes and poor emulsify fatty acids.

D. Impaired mucosal absorption can be resulted from congenital and acquired causes. Basically, main pathogenetic mechanism of malabsorption in such cases is a decrease in surface of nutrients absorption. Pathophysiologic characteristic of selected pathologies with impaired parietal digestion is presented further. Infectious enteritis is not discussed here.

Coeliac disease is a multifactorial chronic autoimmune enteropathy with systemic clinical signs triggered by the ingestion of gluten, the water-insoluble protein fraction in wheat, rye and barley, in patients who are genetically susceptible (HLA-DQ2 or HLA-DQ8 positive). Environmental factors include mode of delivery, presence or absence of breastfeeding, type of diet, use of antibiotics, composition of intestinal microbiota and other factors. Patients with coeliac disease can experience a loss of oral tolerance to gluten any time throughout life. Gluten peptides in the small intestinal lumen translocate the epithelial barrier, via transcellular or paracellular mechanisms and are deamidated by tissue transglutaminase 2 in the lamina propria. Deaminated gliadin peptides are taken up by lamina propria dendritic cells, inducing a proinflammatory gluten-specific CD4+ T-cell response, characterized by IFN-γ and IL-21 production, and anti-gliadin and anti-transglutaminase 2 antibody production by B cells. Activation of the innate immune response is also a key initial step in coeliac disease. Increased epithelial cell stress can upregulate stress molecules on epithelial cells and induce IL-15 production from epithelial cells. IL-15 can induce intraepithelial lymphocytes proliferation and activation and cytotoxic killing of epithelial cells. Commensals or opportunistic pathogens may impair activity of T-regulatory cells, may cause epithelial cell stress, as an increase of intestinal permeability and induction of CD4+ T-cell responses. Immune-mediated damage of enterocytes' villi and death of enterocytes in the proximal parts of the small intestine result in severe malabsorption and diarrhea. Avoidance of gluten-rich products in the diet may improve patient's state.

Lactase deficiency is a relatively infrequent disorder associated by polymorphism of gene encoding lactase. Acquired causes (infectious enteritis, coeliac disease, complications of radiotherapy, etc.) also results in the lactase deficiency. After ingestion of milk or dairy products affected individuals suffer from bloating and diarrhea. These symptoms can be explained by poor degradation of lactose and its ability to stimulate osmotic secretion of the intestinal fluid. In the distal part of the intestine and gut unabsorbed lactose is metabolized by microbiota with for-

mation of short chain fatty acids, CO_2 and H_2S. Avoidance of milk and dairy products should be recommended for the management of lactase deficiency.

Abetalipoproteinemia is a congenital autosomal recessive disorder, which is caused by mutations of gene encoding microsomal triglyceride transfer protein. This protein is necessary for the assembly of chylomicrons in enterocytes. Affected patients have low level of ApoB, triglycerides and chylomicrons in the serum with abnormal transport of lipids to cells. Hemolytic anemia with acantocytosis, poor formation of myelin, ataxia, malabsorption and retinal degeneration are clinical signs of abetalipoproteinemia.

Short-bowel syndrome is resulted from the resection of intestine (due to volvulus, adhesions, or ischemia) or radiation enteritis. Basic mechanisms of malabsorption in patients with short-bowel syndrome include: (1) decreased adhesion surface area; (2) decreased bile salts concentration in the intestine; (3) rapid passage of the chyme through intestine; (4) bacterial overgrowth. Limited resection of the jejunum is better tolerated, whereas ileal resection leads to lack of luminal bile salts and severe malabsorption.

Whipple's disease is a relatively rare multifactorial disease with genetic predisposition, which leads to an abnormal immune response against *Tropheryma whippelii* with systemic inflammation affecting small intestine, joints, heart and central nervous system. Morphologically, intestinal mucosa seems to be atrophic, with its infiltration by macrophages and plasma cells.

E. Impaired nutrients delivery in the blood and lymphatics most commonly reflects primary or secondary lymphangiectasia. The first is a rare congenital disease, whereas secondary relates to lymphoma, tuberculosis, constrictive pericarditis and congestive heart failure with impaired venous and/or lymphatic outflow from the gut. Fat malabsorption is detected; however, significant rise of pressure in the lymphatic capillaries may lead to their rupture and loss of not only lipids, but proteins and lymphocytes with stool.

Clinical symptoms of malabsorption are summarized in the Table 4-5.

Table 4-5. Clinical symptoms of malabsorption

Symptom	Pathogenesis, manifestations
Weight loss	Results from poor absorption of fats, carbohydrates and proteins. Incomplete food starvation will activate gluconeogenesis with secondary weight loss. Appetite is raised compensatory; however, poor absorption can't restore negative energy balance. Weight loss associates with fatigue and muscular weakness.
Micronutrients deficiency	Damage of jejunal mucosa or insufficient emulsifying of fats in the small intestine lead to poor absorption of fat-soluble vitamins A, D, E, K. Vitamin A deficiency manifests by hyperkeratosis, xerophthalmia, night blindness;

	hypovitaminosis D is a cause of rickets in children and osteoporosis in adults; vitamin E deficiency results in oxidative stress and subfertility, whereas vitamin K develops relatively rare, because it is synthetized by intestinal microbiota. Nevertheless, hemorrhagic syndrome due to poor vitamin K-dependent γ-carboxylation of clotting factors in the hepatocytes may develop. Diseases affecting jejunum lead to folates deficiency commonly. Diseases of duodenum and ileum are characterized by insufficient absorption of vitamin B_{12} and vitamin B_{12}-deficiency anemia. Enteritis often results in iron-deficiency anemia, which is explained by the iron malabsorption, sloughing of enterocytes and hemodinamically insignificant bleeding from the gastrointestinal tract. Zn^{2+}, Ca^{2+} и Mg^{2+} deficiency are hallmarks of malabsorption too. They manifest by seizures, arrhythmias and disorders of the central nervous system.
Hypoproteinemia	It is resulted from (1) decreased absorption of amino acids and decreased synthesis of proteins, especially albumins in the liver; (2) loss of albumins with stool in patients with primary or secondary lymphangiectasia. Hypoproteinemia causes negative nitrogen balance, trophic disorders, secondary immunodeficiency and hypooncotic edema.
Diarrhea, bloating	In malabsorption syndrome diarrhea usually osmotic or rare – secretory. Steatorrhea ("fatty stool") reflects fat malabsorption and is characterized by a presence of undigested fatty acids in the stool. Intestinal and gut microbiota hydroxylase these fats, and hydroxylated products stimulate secretory activity of enterocytes. Undigested carbohydrates are fermented by microorganisms with formation of gases which cause bloating. Chronic diarrhea lead to hypokalemia and hypomagnesemia with muscular weakness and arrhythmia.
Neuropathy	It is characterized by disorders of sensitivity and is determined by poor absorption of vitamins of the group B and demyelinization of nerve endings.
Endocrine disorders	They are caused by an abnormal rhythm and amplitude of the tropic hormones secretion from the anterior pituitary due to food starvation and hypoproteinemia. In the first place secretion of gonadotropic hormones will be impaired. This manifests in females by different disorders of menstrual cycle, in males – by decreased libido and impotence. Subfertility may be detected in both sexes.

Intestine and gut motility disturbances

In healthy individuals the average mouth-to caecum transit time is approximately 6 hours and transit through the ascending colon, left colon and sigmoid colon are about 12 hours each. Impaired control of the neuromuscular apparatus of the gastrointestinal tract is a leading cause of disorders of gastrointestinal motility, which if chronic, manifest as nausea, vomiting, bloating, constipation or diarrhea and abdominal discomfort. Normally, neurogenic control of gastrointestinal tract involves central nervous system, autonomic nervous system (parasympathetic and sympathetic) and enteric nervous system. The latter includes approximately 100 million of neurons localized in the myenteric Auerbach's plexus, submucosal Meissner's plexus and pacemaker interstitial cells of Cajal.

Intestinal and colonic disorders due to hypomotility can be classified as following (Table 4-6):

Table 4-6. Causes of slow chyme transit through the intestine and gut

Types	Causes and general characteristics
Extrinsic neuropathic disorders	Damage of autonomic nervous system by trauma, vagotomy, infection (Chagas' disease, cytomegalovirus, Epstein-Barr virus infection), neuropathy (diabetes, amyloidosis) and neurodegeneration (Parkinson's disease, multiple sclerosis) or drug-induced (tricyclic antidepressants, narcotic agents, anticholinergic drugs, antihypertensives, dopaminergic agents). Motor dysfunction often associates with secretory and sensory disturbances. Manifests by constipation.
Enteric and intrinsic neuropathic disorders	Degenerative, immune or inflammatory diseases. Most common is caused by rotavirus, Norwalk virus, cytomegalovirus and Epstein-Barr virus. In these cases inflammatory cells infiltrate myenteric plexus.
Smooth muscle disorders	Systemic sclerosis, amyloidosis, dermatomyositis, dystrophia myotonica and metabolic disorders (hypothyroidism, hyperparathyroidism). Dilation of parts of intesyine or gut associates with bacterial overgrowth.

Commonly slow chyme transit through the small bowel and gut manifests by:

- Stagnation of chyme;
- Bacterial overgrowth;
- Putrefaction of chyme;
- Intestinal endotoxicosis;
- Constipation.

According with Rome criteria, **constipation** can be diagnosed if two or more of the following for at least 12 weeks (not necessarily consecutive) in the preceding 12 months: (1) straining during >25% of bowel movements; (2) lumpy or hard stools for >25% of bowel movements; (3) sensation of incomplete evacua-

tion for >25% of bowel movements; (4) sensation of anorectal blockage for >25% of bowel movements; (5) manual maneuvers to facilitate >25% of bowel movements; (6) <3 bowel movements per week.

This syndrome can be classified into normal-transit constipation, slow-transit constipation and defecatory disorders. Normal-transit or functional constipation is resulted from perceived difficulty from defecation or hardly stool. Defecatory disorders are most commonly due to dysfunction of the pelvic floor or anal sphincter. Slow-transit constipation is caused by alterations in the number of myenteric plexus neurons expressing the excitatory neurotransmitter substance P, abnormalities in the inhibitory transmitters VIP and NO and a reduction in the number of interstitial cells of Cajal, which are thought to regulate gastrointestinal motility. A clinical example of slow-transit constipation is Hirschsprung's disease in which ganglion cells in the distal bowel are absent, a result of an arrest in the caudal migration of neural-crest cells through the gut during embryonic development. The bowel narrows at the area that lacks ganglion cells. Endocrine diseases such as hypothyroidism and hyperparathyroidism may also manifest by slow-transit constipation.

Pathophysiological basis for the management of constipation: (1) diet rich in fibers; (2) bulk laxatives (psyllium, methylceelulose, polycarbophil); (3) osmotic laxatives (magnesium salts); (4) poorly absorbed sugars (lactulose), sugar alcohols (sorbitol, mannitol, polyethylene glycol); (5) stimulant laxatives (senna, castor oil, bisacodyl); (6) mineral oil; (7) rectal enema or suppository; (8) cholinergic agents; (9) prokinetics – 5-HT4-receptor agonists (cisapride); (10) probiotics; (11) biofeedback therapy and patient education; (12) surgery if necessary.

Rapid transit of chyme through the intestine and gut may occur in patients with irritable bowel syndrome (See later), postvagotomy diarrhea, short bowel syndrome, diabetic polyneuropathy and carcinoid diarrhea. These disorders except irritable bowel syndrome lead to poor digestion (due to lack of chyme contact with digestive enzymes), malabsorption and diarrhea.

Diarrhea

Diarrhea is an increase of stool mass more than 250 grams per day with increased contents of the water in the feces more than 60-85%. Classification of diarrhea is presented below:

I. According with mechanisms of development:
   - Osmotic;
   - Secretory;
   - Exudative;
   - Diarrhea due do disorders of gastrointestinal tract motility.

II. According with etiology:
   - Infectious;
   - Non-infectious.

III. According with duration:

- Acute (lasting less than 2-3 weeks);
- Chronic (persisting during 4-6 weeks or more).

Osmotic diarrhea is resulted from increased concentration of osmotically active substances in the lumen of the intestine and gut with subsequent entering of the water according with osmotic gradient. Causes of osmotic diarrhea are following: (1) use of drugs (laxatives with magnesium salts), magnesium-containing antacids causing osmotic gradient; lactulose, cholestyramin, neomycin (2) intake of food products containing osmotic substances xylose and sorbitol (in chewing gums, syrups, etc.) or mannitol; (3) congenital deficiency of disaccharidases leading to carbohydrates malabsorption or acquired causes of carbohydrates malabsorption; (4) exocrine insufficiency of the pancreas. Osmotic diarrhea is stopped usually following 2-3 days of starvation.

Secretory diarrhea occurs, if ability of intestinal epithelial cells to secrete fluid significantly enhances. Infectious secretory diarrhea can be caused by use of some laxatives (senna, castor oil, phenolphtaleine, bisakodil, etc.), some other drugs (cholinergics, cholinesterase inhibitors, thiazide diuretics, etc.); intoxications (arsenic salts, fungal-derived toxins, etc.); hormone-producing tumors, which secrete vasointestinal peptide (VIP), acetylcholine, substance P, serotonin, neurotensin, histamine, bradykinin, adenosine, endothelin-1 and others. Such substances stimulate secretion of the water and electrolytes in the lumen of the intestine. For instance, VIPoma is a tumor originated from pancreatic VIP-secreting cells. VIP stimulates adenylate cyclase in the intestinal epithelial cells with subsequent cAMP-dependent secretion of Na^+, K^+ and water in the lumen of intestine. VIP also inhibits gastric secretion of HCl. That is why clinical signs of VIPoma include severe watery diarrhea, hypokalemia and hypochlorhydria. Secretory diarrhea in patients with gastrinoma, tumor of G-cells in the pancreas or duodenum (Zollinger-Ellisson syndrome) associates with peptic ulcer caused by HCl hypersecretion. Diarrhea can be explained by inactivation of pancreatic enzymes in the intestine in acidic environment with subsequent fat malabsorption and stimulation of secretory activity of enterocytes. Carcinoid syndrome, which is characterized by secretion of excessive amounts of serotonin, bradykinin, substance P and histamine from tumors affecting intestine, gut or bronchi also results in secretory diarrhea. Stimulation of secretory activity of intestinal enterocytes is seen in patients with medullary carcinoma of the thyroid gland, which releases calciotonin and prostaglandins in the systemic circulation.

Rare congenital forms of the non-infectious secretory diarrhea with autosomal recessive type of inheritance were described. These pathologies start even in fetuses and their pregnant mothers will develop hydramnion. Hereditary chloride diarrhea is resulted from mutation of gene, encoding protein of enterocytes' villi which is responsible for the Cl^-/HCO_3^- exchange. Affected patients loose Cl^- with stool, pH of feces shifts to the acidic values, and metabolic alkalosis developing. Congenital diarrhea with excessive Na^+ secretion in the intestine is a result of mutation of gene encoding Na^+/H^+ exchanger in enterocytes.

The classical example of infectious secretory diarrhea is cholera. Cholera enterotoxin consists of A and B subunits. The last is necessary for the firm adhesion of *Vibrio cholera* to enterocytes, whereas the first subunit binds with G-proteins in enterocytes with stimulation of adenylate cyclase. Accumulation of cAMP in enterocytes results in increased secretion of the Na^+, Cl^-, HCO_3^- and water in the lumen. Concentration of such electrolytes in the blood falls. Severe diarrhea (up to 10 L per day) leads to dehydration, electrolyte and acid-base disturbances. Infectious caused by toxigenic strains of *E. coli, Helicobacter jejuni, Yersinia enterocolitica, Clostridium difficile, Staphylococcus aureus,* etc. also manifests by secretory diarrhea.

Exudative diarrhea can be classified into infectious (caused by pathogenic strains of *Shigella, Salmonella, Yersinia, Escherichia, Aeromonas,* etc., some viruses – rotaviruses, adenoviruses, HIV, etc. or protozoa – amoeba) and non-infectious (in patients with ulcerative colitis). Main mechanism of exudative diarrhea is a loss of contacts between adjacent enterocytes. Stool contains not only excessive concentrations of electrolytes and water, but also proteins, leukocytes and erythrocytes. The latter helps to differentiate secretory and exudative diarrhea.

Diarrhea due to motility disorders may be caused by both hypo- and hypermotility of the intestine and gut. Hypermotility is seen in patients with irritable bowel syndrome, dumping syndrome and thyrotoxicosis. Diabetes mellitus complicated with autonomic neuropathy, systemic diseases of connective tissue, or diverticular disease are characterized by decreased intestinal motility and diarrhea. Pathogenesis of diarrhea complicated diabetic neuropathy is following: degeneration of the adrenergic nerve endings in the wall of the intestine and gut → decreased motility → bacterial overgrowth and colonization of proximal parts of the intestine with pathogenic microbiota → deconjugation and dehydroxylation of bile acids by pathogenic microbiota → decreased concentration of bile salts in the intestine → fat malabsorption → hydroxylation of fats by microbiota with formation of substances with amphyphilic properties → stimulation of secretory function of enterocytes → loss of electrolytes and water in the lumen → diarrhea.

Consequences of diarrhea include:

- Dehydration, hypovolemic shock, DIC, and polyorgan failure in severe cases;
- Electrolyte disorders with cardiac arrhythmias;
- Acid-base disorders;
- Malnutrition, weight loss in chronic diarrhea;
- Specific symptoms related to the underlying cause of diarrhea.

In certain circumstances (in young children) diarrhea may be life-threatening.

Pathophysiologic basis for the treatment of diarrhea: (1) management of underlying disease, for instance, antibacterial drugs in diarrhea caused by pathogenic bacteria or protozoa; (2) fluid replacement therapy – parenteral or oral, depending on the severity of diarrhea with electrolytes, glucose or polymeric rice-based solutions, which may be strengthened with enkephalinase inhibitors to increase concen-

tration of enkephalines in the gut with antisecretory activity; (3) drugs suppressing intestinal motility and stimulating absorption of the water and electrolytes (loperamide); however, it should be avoided in patients with bloody diarrhea; (4) surgical treatment of tumors producing secretory diarrhea or in case of inability to remove tumor synthetic analog of somatostatin – octreotid should be administered to suppress secretion of hormone-like substances from the tumor; (5) probiotics in rotavirus diarrhea; (6) correction of malnutrition in patients with chronic diarrhea; (7) new classes of antidiarrheal antisecretory drugs are developed now – blockers of anion channels and antagonists of cAMP-dependent potassium channels of enterocytes.

Inflammatory bowel diseases

Inflammatory bowel diseases (IBDs), including ulcerative colitis and Crohn's disease, are chronic inflammatory multifactorial diseases which are resulted from inappropriate and ongoing activation of the mucosal immune system. This aberrant response is most likely facilitated by defects in both the barrier function of the intestinal epithelium and the mucosal immune system. Comparative characteristic of Crohn's disease and ulcerative colitis is presented in the Table 4-7.

Table 4-7. Crohn's disease vs. ulcerative colitis

Features	Crohn's disease	Ulcerative colitis
Region of involvement	Any portions of gastrointestinal tract	Rectum, colon
Particular features of inflammation	Segmental, transmural, granulomatous inflammation	Continuous, limited to mucosa
Extraintestinal manifestations	Aphtous stomatitis, arthritis, erythema nodosum, digital clubbing, episcleritis, renal stones, gall stones	Pyoderma gangrenosum, sclerosing cholangitis, chronic hepatitis, ankylosing spondylitis
Age at presentation	1^{st} peak – late teens, 2^{nd} peak – late adulthood	
Gender difference	Women are slightly predominate	Men are slightly predominate
Complications	Strictures	Colorectal cancer
Endoscopic findings	Aphtous and linear ulcers, cobblestone appearance, perianal abscesses	Friability of mucosa, pseudopolyps

At least four basic factors are responsible for the development of inflammatory bowel diseases (Fig. 4-13). In fact, IBDs are examples of poor controlled chronic inflammation in the intestine and gut. Mutations or polymorphisms of NOD genes were described firstly as a cause of genetic predisposition for the Crohn's disease. Such genes encode Pathogen Recognition Receptors NOD, which recognize distinct motifs found in the peptidoglycan of bacteria and have a role in signaling of innate defense responses in the host. The cytoplasmic detection system

mediated by NODs likely plays a key role in host defense in those tissues in which Toll-like receptors (TLRs) are absent or expressed at low levels. This occurs in epithelial cells that line mucosal surfaces, for example, in colonic epithelial cells. Activation of NODs leads to activation of NF-kB with subsequent synthesis of pro-inflammatory mediators including proinflammatory cytokines. However, other genetic polymorphisms play role in the pathogenesis of IBDs. Mucosal homeostasis is resulted from balance between effector cells (Th1/Th2/Th17 cells) and T-regulatory cells (T-regs). An increase in the effector cell population with excessive inflammatory responses or a decreased function of regulatory T cells producing anti-inflammatory cytokines (IL-10, TGF-β) can result in mucosal inflammation. For instance, Crohn's disease is characterized by predomination of Th1-mediated immune response, whereas ulcerative colitis is due to Th2-mediated inflammation. The intestinal epithelium acts as a critical mediator of communication between the lumen and the mucosal immune system via the release of cytokines and chemokines that signal the presence of pathogens. This barrier may be disrupted and antigen presenting cells will begin to recognize PAMPs (both from pathogenic microbiota and commensals) with development of uncontrolled severe inflammation. Severe tissue damage will activate myofibroblasts, which secrete components of extracellular matrix thus leading to fibrosis, especially in Crohn's disease. To better understanding pathogenesis of IBDs it is strongly recommended to revise Part IX "Inflammation" in the Textbook "General pathophysiology: the essentials".

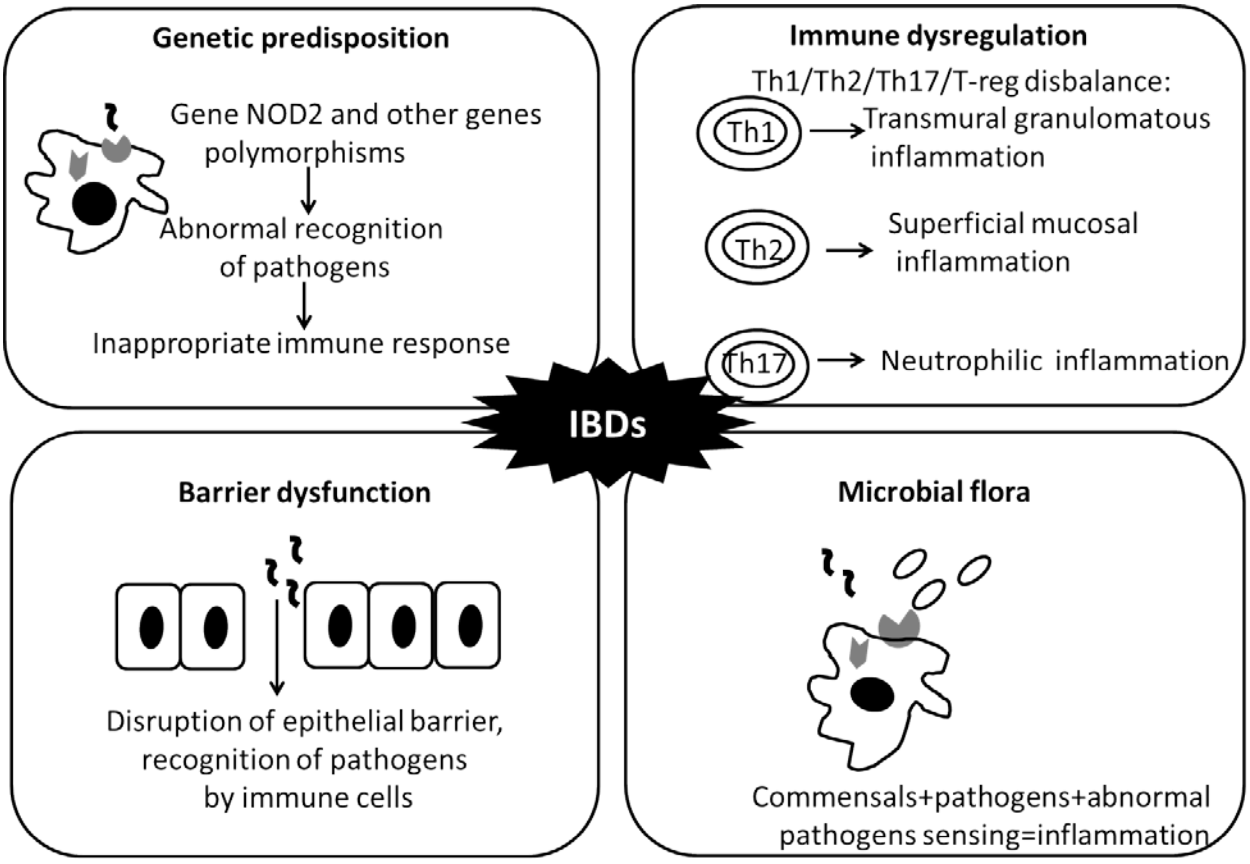


Figure 4-13. Pathogenesis of inflammatory bowel diseases (IBDs): general considerations

Pathophysiologic basis for the treatment of IBDs: to induce and/or maintain remission it is necessary to suppress excessive inflammation in the gastrointestinal tract with several approaches. For instance, sulfasalazine and other 5-amino salicylic acid derivatives prevent activation of transcription factors (NF-Kβ and others) which trigger inflammation. Oral or parenteral glucocorticoids also are able to suppress inflammation. Antibacterial therapy (metronidazole and/or ciprofloxacin) help to eradicate pathogenic microbiota. Cytotoxic agents would be administered if above mentioned treatment is unsuccessful. Azathioprine and 6-mercaptopurine inhibit purine nucleotides synthesis and cell proliferation and decrease immune response. Antimetabolite methotrexate suppresses activity of dihydrofolate reductase, diminishes synthesis of DNA and decreases production of IL-1. Cyclosporine is a lipophilic peptide inhibiting both cellular and humoral immune reactions; it also blocks activity of T-helper cells and their synthesis of IL-2 thus indirectly suppressing activity of B-cells. Similar effects have new macrolide antibiotic tacrolimus. Biological therapy is used now: (1) anti-TNF therapy – using of monoclonal antibodies against TNF-α (infliximab, adalimumab, cetrolizumab); (2) monoclonal antibodies against different subunits of adhesion molecules integrins, which prevent migration of lymphocytes in the site of inflammation (natalizumab). Therapy in development is focused on the manufacturing of monoclonal antibodies against IL-12, IL-23, IL-6; selective adhesion molecules inhibitors, growth factors analogs, antifibrotic agents. Dietary intervention is recommended. Surgical therapy is indicated in some cases.

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is the most common functional gastrointestinal disorder, affecting up to 15% of the general population in the world. Classically, IBS presents with abdominal pain or discomfort that is relieved by defecation or is associated at its onset with a change in stool frequency (either an increase or decrease) or a change in the appearance of the stool (to either loose or hard).

IBS is now recognized as multifactorial disease with genetic predisposition and poor defined pathogenesis. Nevertheless, basic mechanisms of IBS are presented in the Fig. 4-14. IBS is thought to be a polygenic disorder. Polymorphisms or epigenetic regulation of selected genes are involved in the pathogenesis of IBS. Such genes include genes related to the regulation of the HPA axis; female sex hormones receptors; 5-HT signalling system; inflammation related genes and catecholaminergic signalling genes.

Studies performed in patients with IBS have demonstrated abnormalities in brain regions with task-related networks linked to emotional arousal, central autonomic control, central executive control, sensorimotor processing and salience detection. Moreover, it was documented that relapse of both IBS and IBDs are strongly associated with stress (See explanations in the Fig. 4-15).

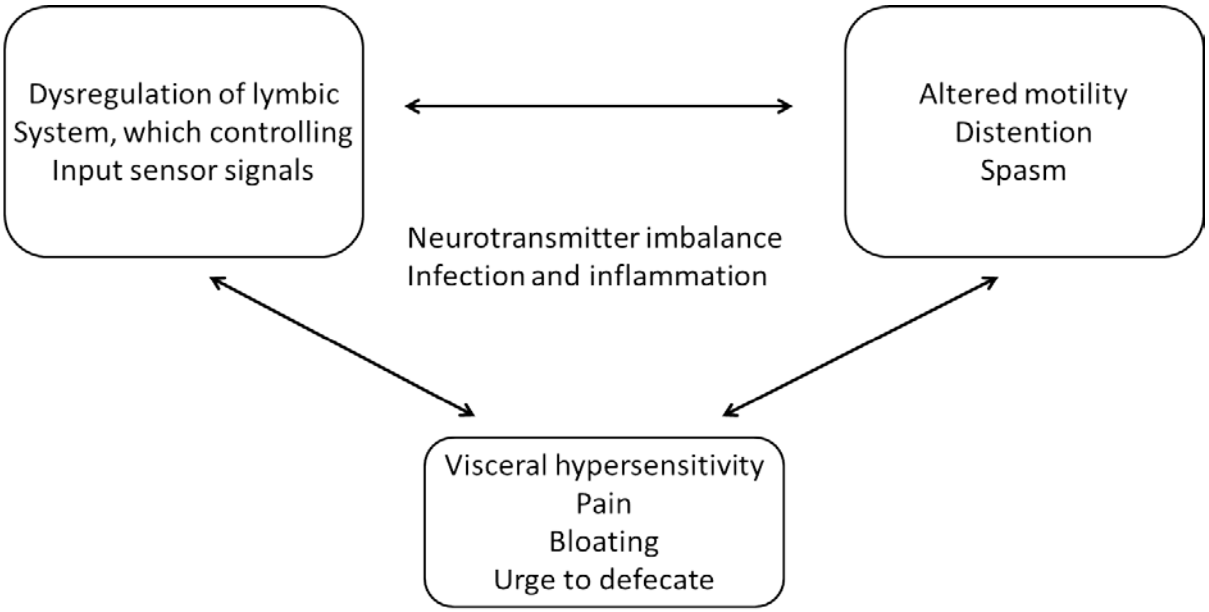


Figure 4-14. Pathogenesis of the irritable bowel syndrome (IBS)

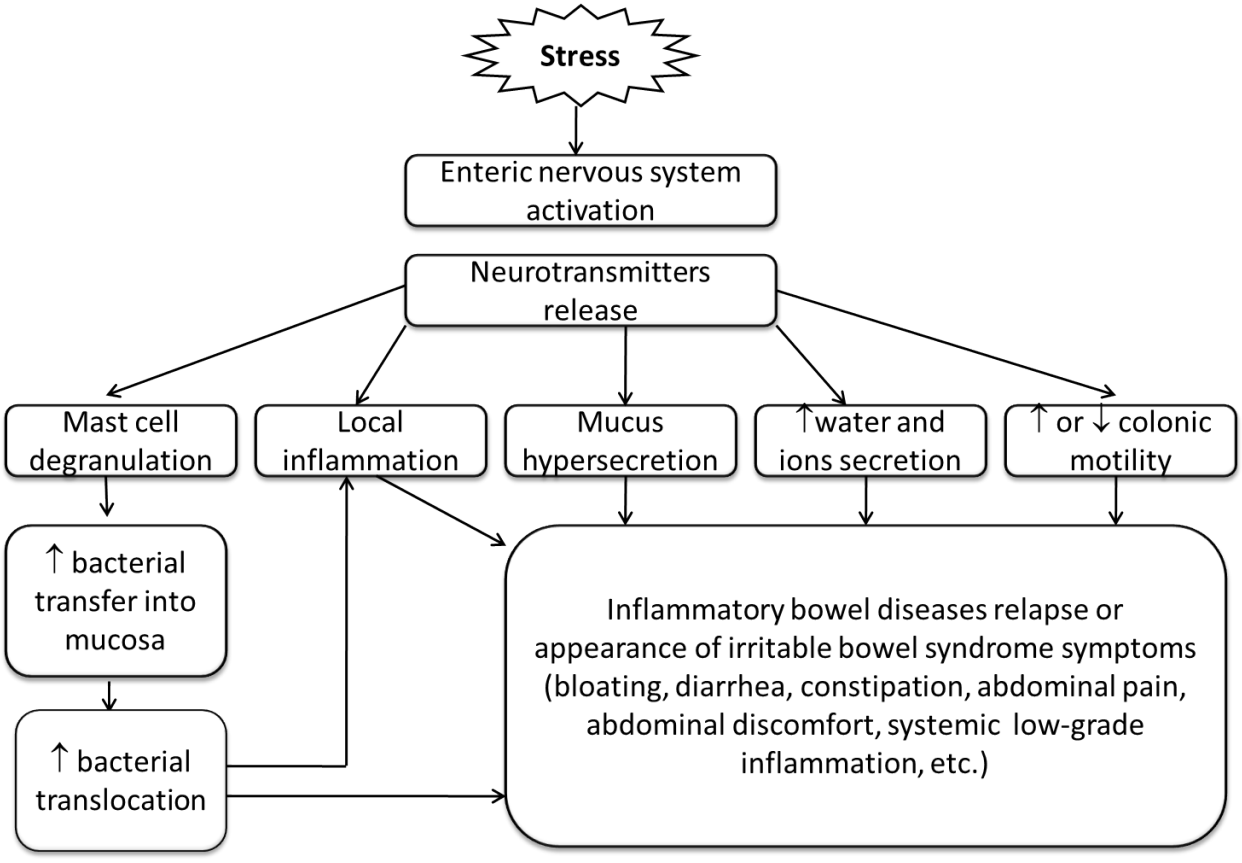


Figure 4-15. The role of stress in the intestinal inflammation

The hypersensitive brain, and presumably enteric nervous system (ENS) producing a net of biologically active substances (acetylcholine, norepinephrine, serotonin, γ-aminobutyric acid, gases NO and CO, peptides – calcitonin-gene related peptide, cholecystokinin, galanin, gastrin-releasing peptide, neurotensin, neuropeptide Y,

neuromedin U, opioids, peptide YY, somatostatin, substance P, VIP and others), shows increased responses to a variety of viscerosensory and exterosensory stimuli, which by themselves might not be consciously perceived in healthy individuals or in patients with inflammatory bowel disorders in whom intact descending inhibitory bulbospinal influences reduce dorsal horn excitability. This hyper-responsiveness might be a primary genetic or epigenetic alteration in certain brain networks. An altered brain networks produce abnormal signals. The chronically increased ANS output, results in an extensive remodeling of various peripheral cells in the immune system, ENS, gut epithelium (permeability), and in the composition and function of the gut microbiota, all contributing to sensitization of visceral afferent pathways, and increased viscero sensory feedback to the brain.

An altered composition of the gut microbiota, or the mediators produced by these gut microbiota, might influence epithelial permeability, possibly by degrading epithelial tight junction proteins such as occludin. Also, the gut microbiota can influence the activity of enteroendocrine cells. Additionally, gut microbiota, or their metabolites, can directly affect the cells of the immune system, inducing increased immune activity. Cytokines and other mediators secreted by immune cells, as well as mediators secreted by the gut microbiota and enteroendocrine cells, can leave the mucosa via the blood stream and have systemic effects, for instance, systemic low grade inflammation.

Pathophysiologic basis for the treatment of IBS: (1) patient education; (2) diet depending on the clinical form of IBS; (3) antispasmodics – anticholinergic drugs to reduce abdominal pain; (4) antidiarrheal agents in case of diarrhea-predominant variant; (5) psychotherapy and/or antidepressant drugs; (6) antiflatulence agents; (7) modulation of gut microbiota with antibiotics and/or probiotics; (8) serotonin receptor agonists or antagonists depending on the form of IBS.

Intestinal obstruction (ileus)

Intestinal obstruction (ileus) is a disorder of movement of intestinal contents in a cephalocaudal direction. It can be acute or chronic and may affect the small intestine (high or low intestinal obstruction) or colon. Classification of acute intestinal obstruction, which is potentially life-threatening disorder without urgent surgery, is presented in the Fig. 4-16. Chronic intestinal obstruction most commonly affects colon and may last even several months.

Mechanical obturation can result from a tumors, foreign bodies, coprolites or helminthes. Strangulated ileus is caused by strangulation of hernia (inguinal, femoral, or umbilical) and postoperative adhesions which compress any portion of the bowel with mesentery and arterial blood vessels followed with necrosis of affected bowel and its perforation. Strangulated ileus also may be due to volvulus or complete twisting of the bowel on an axis formed by its mesentery. Volvulus most commonly affects the cecum. Intussusception is a telescoping of bowel with smaller diameter into the adjacent segment (for instance, terminal ileum into the right colon). Intussusception is a relatively frequent form of the acute ileus in before 2 years of age.

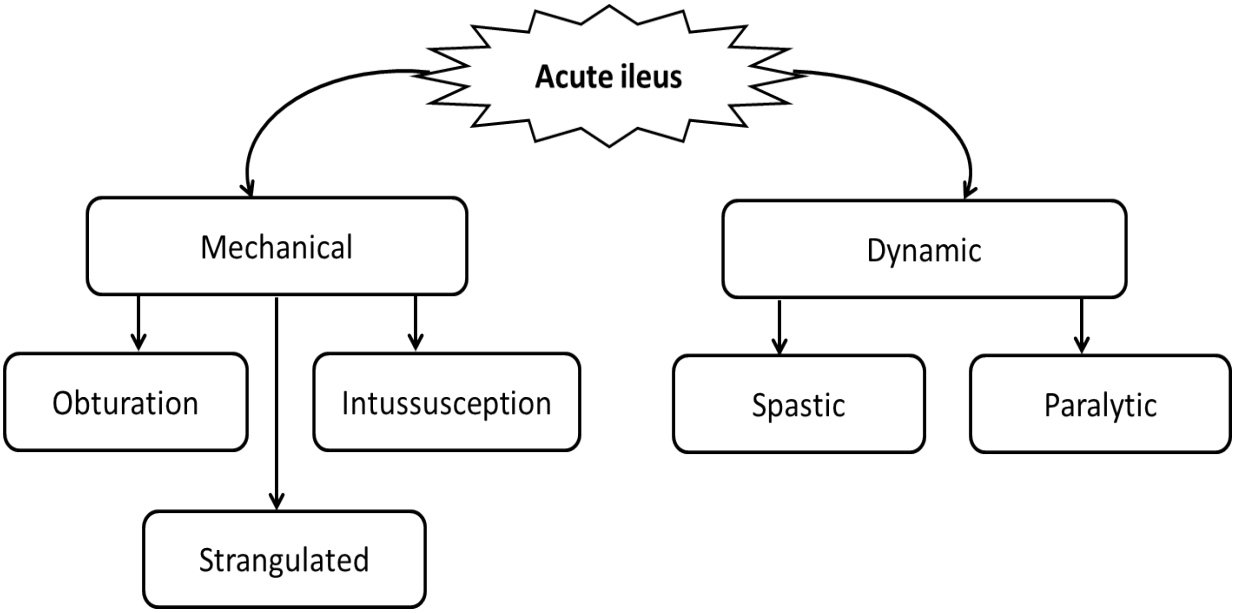


Figure 4-16. Classification of the acute intestinal obstruction (ileus)

Dynamic acute mechanical obstruction is resulted from disorders of intestine or gut motility. Spastic ileus, or excessive contraction of segments of intestine and gut, may develop during different intoxications, for example, with lead salts and other heavy metals. Paralytic, or adynamic ileus, is due to suppression of peristalsis after abdominal surgery, in inflammatory diseases affecting abdominal cavity, vascular diseases affecting intestine and gut, pelvic fractures, and back trauma. Paralytic ileus develops relatively early in patient with peritonitis. Irritation of mesenteric nerve plexus with bile or bacterial toxins as hypokalemia and intestinal ischemia may also impair motility of the intestine and gut. Diseases affecting enteric nervous system and smooth muscles of the intestine and gut are other causes of the paralytic ileus.

Clinically, acute ileus starts with pain, absolute constipation, abdominal distention, and vomiting. Late manifestations which may be encountered include dehydration, oliguria, hypovolemic shock, pyrexia, septicaemia, respiratory distress and peritonism. Pathogenesis of acute ileus is summarized in the Fig. 4-17. Irrespective of etiology or acuteness of onset, the proximal bowel dilates and develops an altered motility. Below the obstruction, the bowel exhibits normal peristalsis and absorption until it becomes empty, when it contracts and becomes immobile. Initially, proximal peristalsis is increased to overcome the obstruction, with the length of time it remains vigorous being proportional to the distance of the obstruction. If the obstruction is not relieved the bowel begins to dilate causing a reduction in peristaltic strength, ultimately resulting in paralysis. The distension proximal to an obstruction is produced by two factors: (1) by gas (CO_2, nitrogen, H_2S) due to bacterial overgrowth; (2) by fluid. Loss of fluid during acute ileus can be explained by several mechanisms: accumulation of fluid in the lumen of the bowel (or so-called “third-space”), reduced oral intake of fluid due to severe pain, defec-

tive intestinal fluid absorption, and loss of fluid with vomiting.

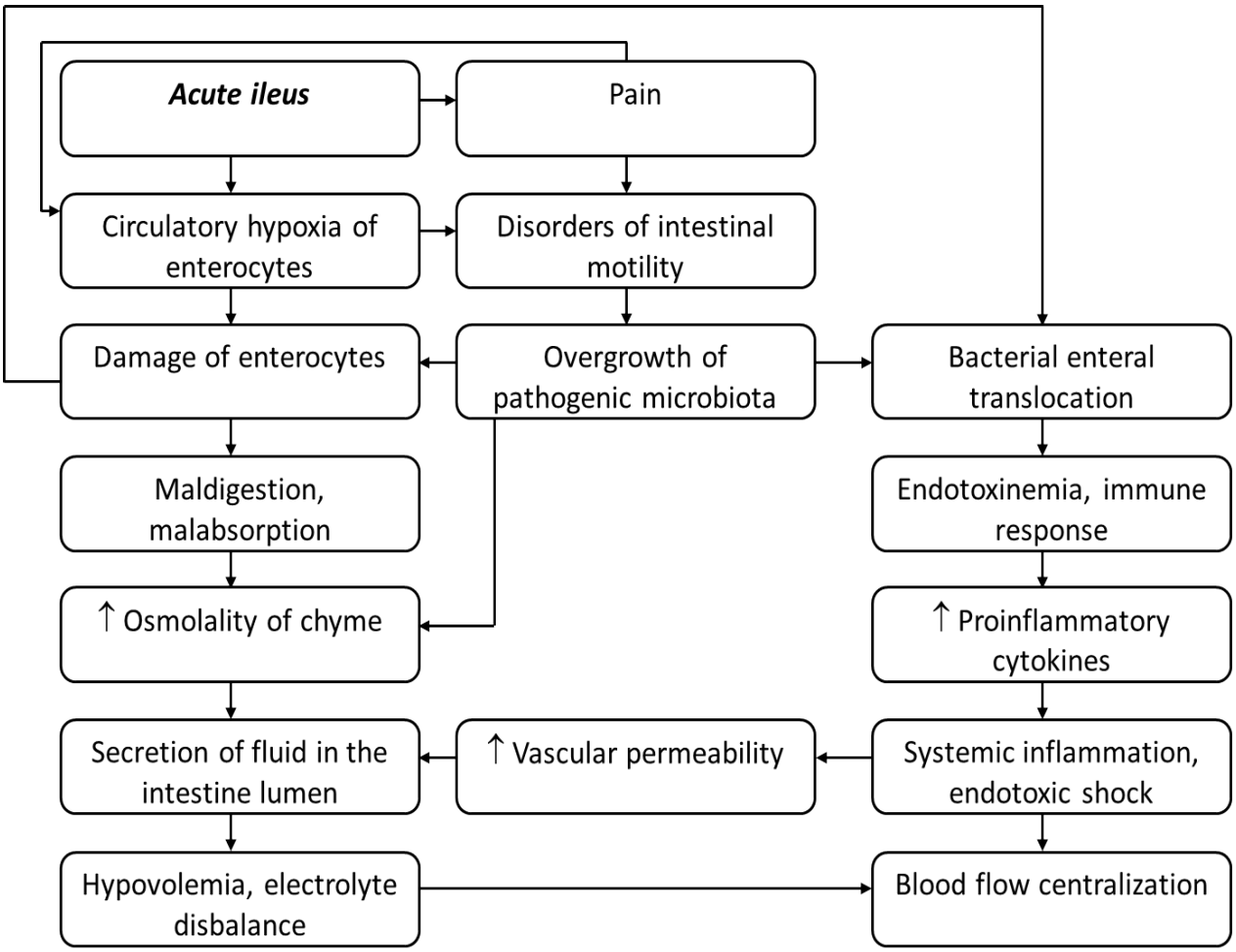


Figure 4-17. Simplified pathogenesis of the mechanical intestinal obstruction (ileus)

Treatment of acute ileus depends on the cause and type of obstruction. Most cases of paralytic obstruction respond to decompression of the bowel through nasogastric suction and correction of fluid and electrolyte imbalances. Strangulation and complete bowel obstruction require emergency surgical manipulations. Following relief of obstruction, the viability of the involved bowel should be carefully assessed. Broad-spectrum antibiotics should be administered.

Pancreatitis

Pancreatitis is an inflammatory disease of the pancreas with predominant injury of pancreatic acini. Pancreatitis can be acute or chronic.

Acute pancreatitis. Normally, pancreatic cells are protected from autodigestion by different mechanisms: (1) digestive pancreatic enzymes are produced as proenzymes; (2) subcellular compartments producing zymogenic granules are anatomically separated; (3) proenzymes in the secretory granules are packed in complex with proteases inhibitors and surrounded by protein paracrystalline; (4) zymo-

genic granules contain relatively low concentration of ionized calcium and contents of these granules has acidic pH thus preventing premature intracellular activation of proenzymes in pancreatic cells. Fail of these mechanisms leads to intracellular conversion of proenzymes in their active form and autodigestion of pancreatic cells.

Causes of acute pancreatitis are exogenous and endogenous. Exogenous causes are following:

- Alcohol abuse, especially with underlying cholelithiasis;
- Viral infections (mumps, rubella, cocksackievirus, cytomegalovirus, Epstein-Barr virus, HIV, etc.), some bacterial and parasitic infections;
- Blunt abdominal trauma, abdominal surgery;
- Drugs (immunosuppressive azathioprine; thiazide diuretics, furosemide; antibacterial tetracycline, sulfonamides, metronidazole; steroids – estrogens, corticosteroids; valproic acid);
- Exposure of venoms (scorpion) and toxins (some metal salts, methanol)

Endogenous causes of acute pancreatitis are:

- Biliary tract disease, which leads to obstruction of the common bile duct with gallstones and/or bile reflux into pancreatic ducts, edema or spasm of Oddi's sphincter;
- Metabolic abnormalities including hyperlipidemia types I, IV and V; hypercalcemia in patients with hyperparathyroidism; uremia; eclampsia in pregnancy; diabetic ketoacidosis, etc.;
- Penetrating duodenal ulcer;
- Shock of any etiology, vascular diseases affecting pancreas, thrombosis or embolism of pancreatic blood vessels.

If underlying cause of acute pancreatitis is not revealed, pancreatitis is thought to be idiopatic. However, most common causes of acute pancreatitis are episode of heavy drinking and biliary tract disease.

Pathogenesis of acute pancreatitis can be explained as following steps:

1. Pathogen exposure → universal molecular mechanisms of exocrine pancreatic cells injury (ATP deficiency, oxidative and nitrozative stress, accumulation of ionized intracellular calcium) → damage of intracellular microtubules and miofilaments in pancreatic exocrine cells → delayed release of zymogenic granules in pancreatic ducts → mixture of lysosomal contents and zymogenic granules contents → intracellular activation of trypsinogen and its conversion to trypsin → cascade of activation of other proenzymes and synthesis of set of biologically active substances (Fig. 4-18).
2. Trypsin activates pancreatic lipase, which in turn, damages cellular membrane of pancreatic cells causing their fat necrosis and releasing of DAMPs. After recognition of these molecular patterns by antigen presenting cells, macrophages, monocytes, endothelial cells they begin to produce proinflammatory mediators including proinflammatory cytokines IL-1, IL-6, IL-8, TNF-α with systemic manifestations of acute pancreatitis. Trypsin also acti-

vates phospholipase A2 (PL A2). It leads to destroying of lecithin in cellular membranes with formation of lysolecithin which augments damage of cellular membranes. Trypsin also facilitates conversion of pancreatic proelastase to its active form. Elastase impairs integrity of vascular wall in pancreatic blood vessels thus increasing vascular permeability and stimulating edema formation. Pancreatic edema produces severe abdominal and back pain. Moreover, trypsin mediates formation of kallikrein and bradykinin.

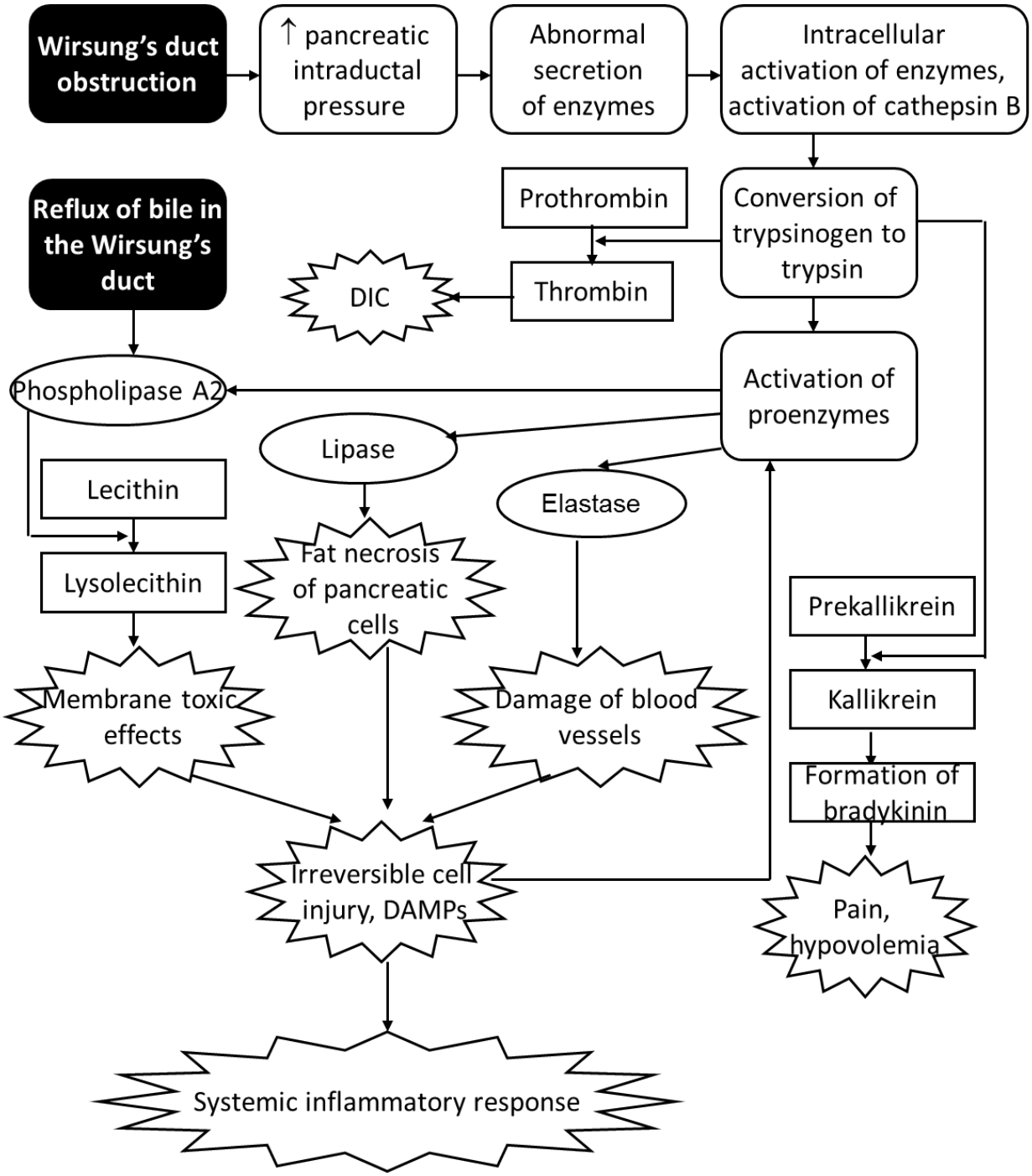


Figure 4-18. Pathogenesis of acute pancreatitis

DAMPs, damage associated molecular patterns; DIC, disseminated intravascular coagulation

These proinflammatory mediators and proinflammatory cytokines IL-1, IL-6, IL-8, TNF-α activate inducible NO-synthase with net of effects: generalized vasodilation, increased vascular permeability, more severe pancreatic edema and arterial hypotension. Bradykinin also activates its receptors creating intolerable pain. Trypsin also catalyzes conversion of prothrombin to thrombin, which together with proinflammatory cytokines, activated platelets, endothelial dysfunction cause disseminated intravascular coagulation.

3. Appearance of zymogenic granules contents in the interstitial space of the pancreas results in the recruitment of leukocytes in the site of inflammation. Subsequent activation of neutrophils and macrophages with releasing of ROS, RNS, cathepsins B, D, G, collagenases and elastase with proteolytic activity from them will amplify inflammatory response. "Cytokine storm" which is characterized by hyperproduction of IL-1, IL-6, IL-8, TNF-α leads to systemic inflammatory response.

Acute pancreatitis caused by different causative factors has specific pathogenetic features.

Alcohol-induced pancreatitis. Ethanol stimulates exocrine pancreatic secretion and spasm or edema of Oddi's sphincter with subsequent rise in intraductal pressure. Activation of ethanol-metabolizing pathway in the pancreas provokes oxidative stress and oxidative-mediated damage of pancreatic acinar cells.

Pancreatitis associated with biliary tract disease more common affect females because gallstone disease is more specific for them. Obstruction of bile duct results in reflux of bile in the Wirsung's duct and injury of pancreatic acinar cells. Bacterial toxins from the bile via lymphatics may also travel to the pancreas potentiating inflammation.

Pancreatitis associated with hypercalcemia (in hyperparathyroidism, hypervitaminosis D, multiply myeloma) can be explained by two independent mechanisms: precipitation of calcium in the pancreatic juice with plug formation and rise in the intraductal pressure and calcium-dependent activation of trypsinogen conversion to trypsin.

Pancreatitis associated with hyperlipidemia, especially with elevated level of chylomicrons is due to free fatty acids, whose concentration elevates after action of pancreatic lipase. Free fatty acids may damage acinar pancreatic cells.

Morphologically acute pancreatitis is illustrated by acute edema of the pancreas, hemorrhagic necrosis, fat necrosis and infected pancreatic necrosis. At least 25% of affected individuals develop potentially life-threatening systemic complications (Table 4-8).

Table 4-8. Pathogenesis of systemic complications of acute pancreatitis

Mechanisms	Systemic complications
Activation of PL A2, elastases, carboxypeptidases, trypsin, chymotrypsin → necrosis of pancreatic acinar	Hypovolemic shock, acute renal failure

cells, activation of kallilrein-kinin system, complement system, "cytokine storm", activation of the constitutive and inducible NO-synthases → vasodilation, increase of vascular permeability, increase of the bowel wall permeability, exudation of fluid in the retroperitoneal space and in the abdominal cavity	(prerenal azothemia), pancreatic ascites
Disorders of pulmonary microcirculation (DIC), noncardiogenic toxic pulmonary edema, degradation of the surfactant by activated PL A2, uncontrolled inflammation	Acute respiratory distress syndrome (ARDS), acute respiratory insufficiency
Activation of proteolytic enzymes, accumulation of toxins, proinflammatory cytokines in the blood, oxidative and nitrozative stress → toxic brain injury	Metabolic encephalopathy
Releasing of tissue factor (TF), activation of blood coagulation, activation of platelets with generalized thrombosis, activation of fibrinolysis and bleeding at the final stage	Disseminated intravascular coagulation (DIC)
Action of elastases, PL A2, proinflammatory cytokines, toxins, ROS, RNS with hypocoagulation at the final stage of DIC → damage of vascular wall, increase of vascular permeability	Gastrointestinal bleeding, skin bleeding
Precipitation of calcium with free fatty acids in the pancreas → hypocalcemia, seizures Injury of pancreatic cells → release of potassium → hyperkalemia → fluid replacement therapy → hypokalemia Hypovolemia, shock, generalized hypoperfusion → lactic metabolic acidosis Extensive pancreatic necrosis, death of pancreatic β-cells → insulin deficiency → ketoacidosis ARDS → respiratory acidosis	Electrolyte disorders and acidosis

Acute pancreatitis may also complicate with infected pancreatic necrosis, pancreatic abscess or inflammatory pseudocysts.

Pathophysiologic basis for the treatment of acute pancreatitis depend on its severity and include: (1) pain control (sometimes with parenteral narcotics); (2) nasogastric suction to remove gastric juice which normally stimulates pancreatic secretion; (3) fluid replacement therapy; (4) prevention and treatment of complications; (5) broad spectrum antibiotics in proved infectious complications; (6) surgery if necessary.

Chronic pancreatitis is a chronic inflammatory disease of the pancreas with its irreversible morphological changes (exocrine cells atrophy, fibrosis of parenchyma and obliteration of pancreatic ducts), exocrine and endocrine pancreatic insufficiency.

Etiology of chronic pancreatitis:

- Chronic alcoholism is a cause of at least 60% of all cases of chronic pancreatitis. Ethanol stimulates proteins secretion by pancreatic acinar cells and suppresses water and bicarbonates secretion by these cells. Viscosity of pancreatic secretion increases which provokes formation of protein precipitates in the pancreatic ducts. Main proteins of these precipitates are lithostathine and GP2 proteins. At normal conditions, lithostathine is produced by acinar pancreatic cells. It prevents formation of crystals of calcium carbonates in the pancreatic ducts. In patients regularly consumed alcohol formation of normal lithostathine decreases, but synthesis of abnormal lithostathine S1, in contrast, increases. The latter is poor soluble in the pancreatic juice at neutral pH thus stimulating formation of stones in the pancreatic ducts. Moreover, repeated use of alcohol causes oxidative stress in pancreatic acinar cells. Combined with undernutrition deficiency of natural antioxidants it leads to necrotic death of pancreatic acinar cells. Non-oxidative pathway of ethanol metabolism in the pancreas results in accumulation of ethyl esters of free fatty acids which also damage acinar cells. Chronic injury of pancreatic cells activates proliferation of mesenchymal cells in the pancreas, stimulates macrophages to produce growth factors with excessive formation of extracellular matrix proteins – collagen, fibronectin and proteoglycans with fibrosis of the parenchyma.
- About 30% of all cases of chronic pancreatitis are unrecognized. Probably, the idiopathic chronic pancreatitis has genetic backgrounds. Some patients have mutations of genes encoding trypsinogen with cationic properties. In affected individuals activated trypsin can't be inactivated with proteases inhibitors and triggers autodigestion of pancreatic cells. Other patients have mutations of serine protease inhibitor gene. Chronic pancreatitis also may develop in patients with cystic fibrosis, because mutations of the CFTR gene (Cystic Fibrosis Transmembrane Regulator) would lead to abnormal chlorine transport through cellular membranes.
- Obstruction of pancreatic ducts may be inherited or acquired (obstruction with gallstones, trauma, tumor of pancreatic ducts, etc.). Increase of intraductal pressure could lead to injury of pancreatic cells and fibrosis.
- Metabolic factors (dyslipoproteinemias, hypercalcemia), toxins or drugs (See above).
- Autoimmune-mediated pancreatitis may be primary (without any association with preexisting autoimmune diseases) or secondary (complicated primary biliary cirrhosis, primary sclerosing cholangitis, Sjogren syndrome, etc.).

Chronic pancreatitis manifests by abdominal pain, nausea, vomiting, weight loss, malabsorption (See above), hyperglycemia and jaundice. It can lead to endo-

crine insufficiency and diabetes mellitus due to insulin deficiency, pseudocysts and pancreatic ductal adenocarcinoma.

Pathophysiologic basis for the treatment of chronic pancreatitis: (1) stopping alcohol and tobacco; (2) diet; (3) pain control if necessary; (4) correction of maldigestion, malabsorption and related symptoms; (5) replacement therapy with pancreatic enzymes; (6) treatment of complications; (7) surgery if necessary.

PART V. PATHOPHYSIOLOGY OF THE LIVER

To better understanding pathophysiology of the liver it is important to represent the structural unit of the liver (Fig. 5-1).

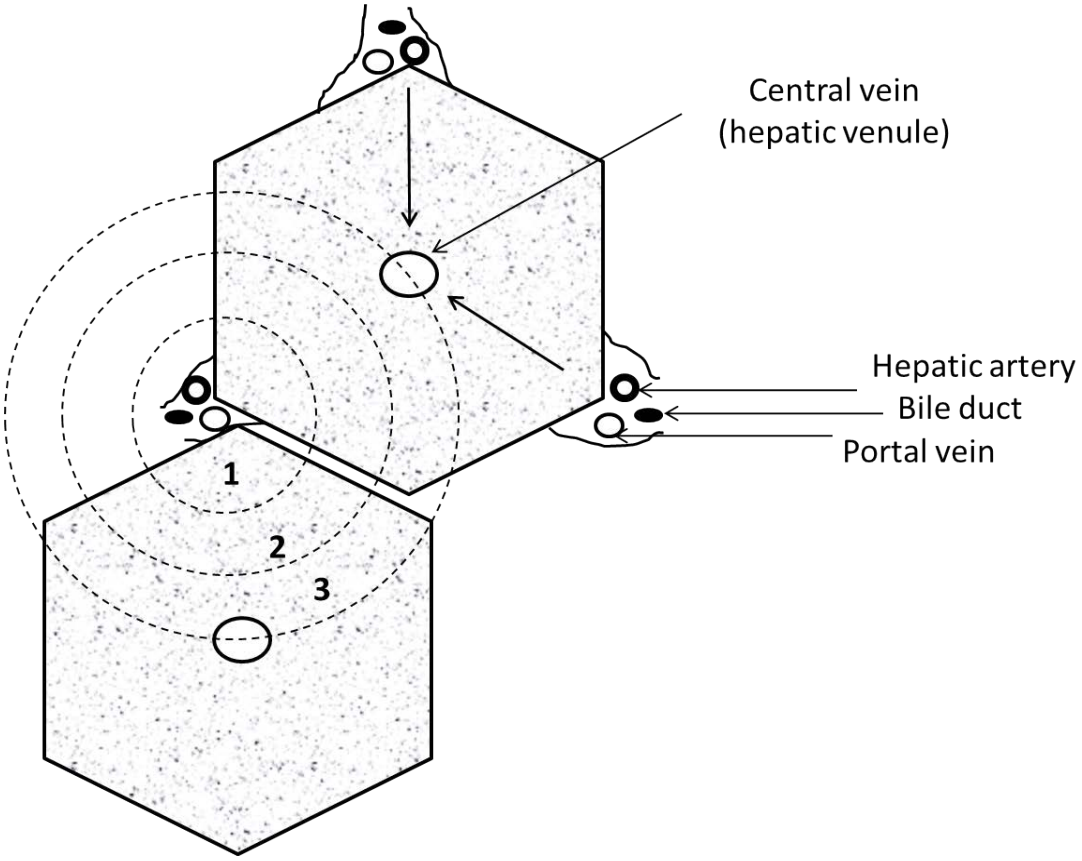


Figure 5-1. Diagrammatic illustration of the hepatic lobule and hepatic acinus

Hepatic lobule (hexagon in the Fig. 5-1) arranges round a single central hepatic vein. Lobule receives hepatic arterial blood with oxygen saturation approximately 95% and portal venous blood with oxygen saturation near 85%, and its bile drains into small bile ducts. Direct lines in hexagon indicate direction of blood flow in the lobule. Alternatively, the acinus arranged around the terminal hepatic artery and terminal portal venule. The acinus is subdivided into three functional zones indicated with dashed rings in the Fig. 5-1. Hepatocytes of zone 1 (periportal zone) receive blood rich in oxygen and nutrients; that is why they are most metabolically active in gluconeogenesis, oxidative phosphorylation and synthesis of urea. However, such hepatocytes receive highest concentrations of "bad" substances – drugs and toxins absorbed in the gastrointestinal tract and such toxic substances from the affluent blood will affect mostly hepatocytes of zone 1. Hepatocytes from zone 2 (mid-zone) and zone 3 (perivenular zone) receive less oxygen; glycol-

ysis and lipogenesis occur predominantly in these hepatocytes. Due to receiving of less oxygen, hepatocytes of zone 3 are most susceptible to hypoxia, for instance, as a result of blood centralization during shock, or following prolonged passive hyperemia in patients with right-sided or total heart failure. Hepatocytes of zone 3 also are sensitive to toxins generated during metabolic reactions in the liver. On the one hand, the dual blood supply to the liver partially protects it from hypoxic injury, but on the other hand, it facilitates metastatic spreading of different malignant tumors in the liver.

Another particular feature of the liver is its good ability to regeneration, which was historically described in the myth about Prometheus' punishment. Uncontrolled nodular regeneration of the liver as a part of inflammation resolution is an essential component of liver cirrhosis.

The liver performs multiply functions in humans. First of all, it actively participates in the metabolic reactions. Carbohydrate metabolism (consumption of glucose and synthesis of glycogen, gluconeogenesis and glycogenolysis, reactions of tricarbonic acid cycle), lipid metabolism (cholesterol synthesis and secretion, fatty acids degradation, VLDL formation; HDL and LDL taking; β-oxidation of fatty acids; formation of ketone bodies), protein metabolism (amino acids desamination, conversion of the ammonia to the urea; amino acids transamination and synthesis de novo; synthesis of proteins) occur in the liver. The liver pursues protective and detoxicative functions: ammonia detoxication; detoxication of xenobiotics; synthesis of glutathione; destruction of damaged cells, proteins, hormones, clotting factors, destruction of microorganisms and antigens arriving in the liver through the portal vein pass in it. The liver also participates in the dilution, transport and deposition of different chemicals. Biotransformation of xenobiotics with excretion of products in the bile; emulsification of fat and vitamins A, D, E, K with bile salts; uptake and storage of vitamins A, D, B_{12} and folates; synthesis of transport proteins occur in this organ. That is why morphological damage of the liver may lead to different metabolic abnormalities. Pathophysiologic characteristic of basic syndromes in liver pathology are presented below.

Jaundice (icterus)

Jaundice (icterus) is a clinical and laboratory syndrome which is characterized by yellowish coloration of skin and mucosa due to abnormal bilirubin metabolism. To better understanding of causes and mechanisms of jaundice it is necessary to summarize bilirubin metabolism in physiological conditions. Bilirubin is a product of heme released from hemoglobin after dying of senescence erythrocytes and other heme-containing proteins (myoglobin, catalase, peroxidase, cytochromes, NO-synthases, etc.) metabolism. After degradation of hemoproteins heme is released. The enzyme hemoxygenase in macrophages in the liver and spleen converts heme to the biliverdin and carbon monoxide CO in equimolar concentrations with subsequent reduction of biliverdin to the bilirubin by the enzyme

biliverdin reductase. After binding of this bilirubin with albumins it is transported in the hepatocytes. This bilirubin is called as indirect (due to its ability to indirectly react with Ehrlich's diazo reagent, Table 5-1) and unconjugated (or unbound with glucuronic acid). From the cytoplasm of hepatocytes indirect, unconjugated bilirubin is transported in the endoplasmic reticulum by transport protein ligandin. In the endoplasmic reticulum enzymes uridine monophosphate-glucuroniltransferase (UMP-GT) and uridine diphosphate-glucuroniltransferase (UDP-GT) catalyze conversion of unconjugated bilirubin to conjugated bilirubin.

Table 5-1. Properties of conjugated vs. unconjugated bilirubin

Parameters	Bilirubin	
	Unconjugated	Conjugated
Ability to bind with albumins	+	-
Van den Bergh reaction with Ehrlich's diazo reagent	Indirect	Direct
Ability to conjugate with glucuronic acid	-	+
Water solubility	-	+
Lipids solubility	+	-
Concentration in the blood serum (total bilirubin - 2-20,5 μmol/L or 0,2-1,2 mg/dL)	< 12 μmol/L (0,2-1,2 mg/dL)	< 7 μmol/L (0,1-0,4 mg/dL)

Conjugated bilirubin is also termed as direct; because of it is unbounded with albumins and directly reacts with Ehrlich's diazo reagent. Main goal of bilirubin conjugation with glucuronic acid is to enhance its water solubility for excretion with bile. Further conjugated bilirubin is transported in the bile ducts via ATP-dependent transport by the **M**ultidrug **R**esistance **P**rotein 2 (MRP2). With bile bilirubin is excreted in the duodenum and passes through the small intestine. Small part of this bilirubin is reabsorbed by mesenteric veins and in the liver destructed to dipyrroles. Most part of bilirubin reaches the terminal ileum and the colon where microorganisms reduce bilirubin to mesobilinogen and stercobilinogen. Some part of stercobilinogen is absorbed via hemorrhoidal veins and appears in the urinary bladder, where it is called as urobilinogen. Its oxidized form in the urine is urobilin. Oxidation of stercobilinogen to stercobilin gives a specific colour for feces. Schematically metabolism of bilirubin is depicted in the Fig. 5-2.

Classification of icterus is presented below.

I. Jaundice (icterus) can be physiological or pathological. Physiological jaundice is seen in almost all borne at term infants during the first week after delivery with more marked skin and mucosa coloration in preterm newborns due to enhanced turnover of red blood cells.

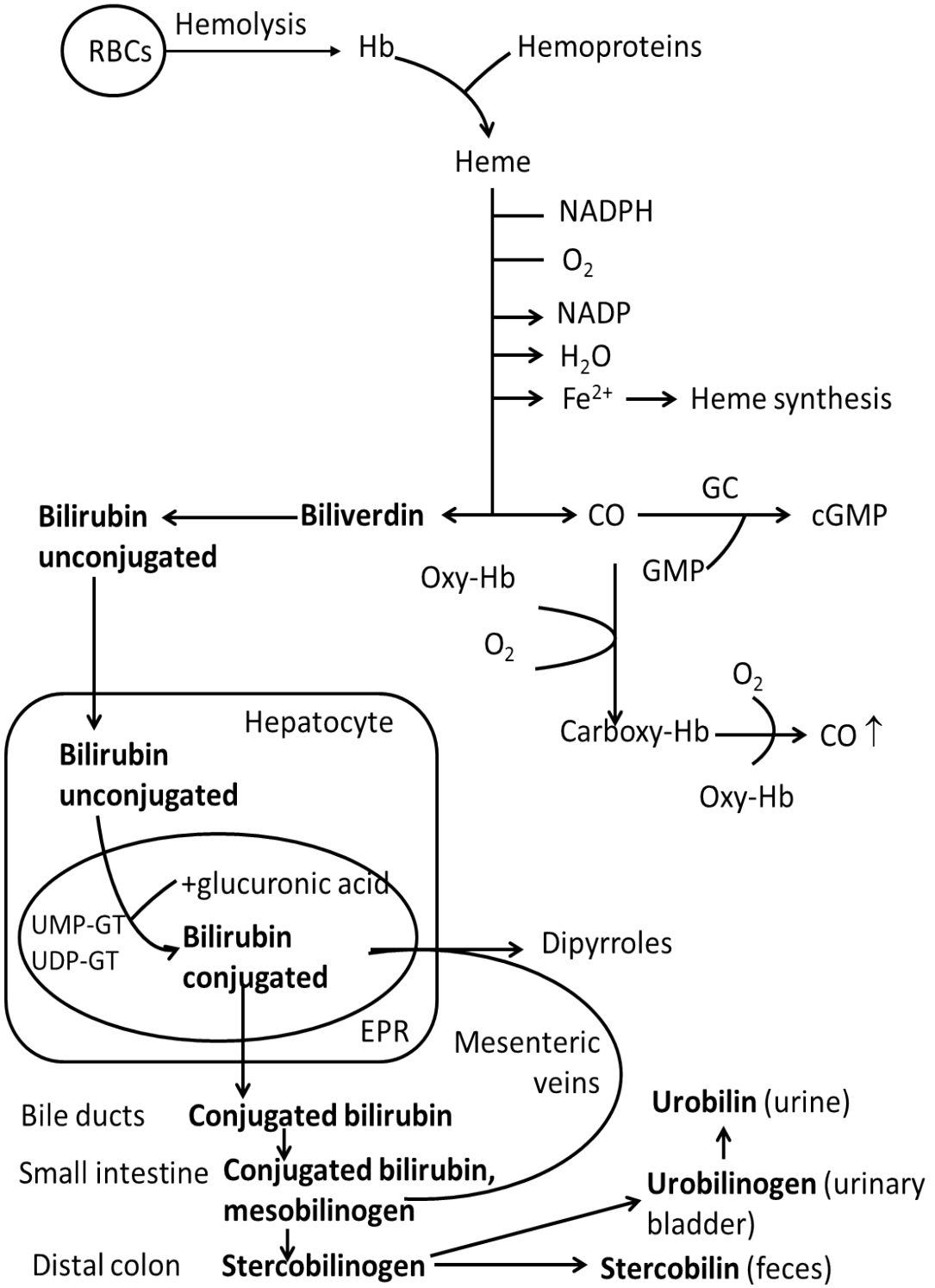


Figure 5-2.Metabolic pathway of bilirubin formation (according with A.J.J. Wood, 2001)

cGMP, cyclic GMP; GC, guanylate cyclase; EPR, endoplasmic reticulum; RBCs, Red Blood Cells; UMP-GT, uridine monophosphate-glucuroniltransferase; UDP-GT, uridine diphosphate-glucuroniltransferase.

Normally newborns have increased RBCs count compared with adults, and life span of their erythrocytes is shorter. Moreover, hepatocytes in newborns have limited ability to conjugate all bilirubin. That is why newborns have predominantly unconjugated hyperbilirubinemia.

Pathological jaundice may occur if:

- Excessive rate of destruction of hemoproteins occurs, when unconjugated bilirubin is not readily converted to its conjugated form;
- Activity of UMP-GT and/or UDP-GT is reduced;
- Transport of conjugated bilirubin in the bile ducts is affected;
- Bile ducts are damaged;
- Several causes exist.

II. Measurement of bilirubin concentration in the blood serum is useful for detection of jaundice in the clinical practice. Depending on predomination of conjugated or unconjugated bilirubin jaundice is usually classified into jaundice with predominantly conjugated or unconjugated hyperbilirubinemia (See below).

III. Depending on the basic mechanism and level of bilirubin metabolism disorders jaundice can be classified into:

- Hemolytic (overhepatic);
- Hepatic (parenchymal);
- Obstructive (underhepatic).

Jaundice with predominant unconjugated hyperbilirubinemia is detected in several pathologies:

- Hemolytic anemias;
- Abnormal unconjugated bilirubin uptake by hepatocytes in Gilbert's disease, icterus neonatorum, or after use of some drugs (rifampin, flavispidic acid or roentgen-contrast substances);
- Impaired conjugation of bilirubin with glucuronic acid in Gilbert's disease, Crigler-Najjar syndrome and icterus neonatorum.

Main pathogenetic mechanism of this type of jaundice is impaired formation of bilirubin glucuronides. Unconjugated bilirubin has high lipids solubility; that is why it causes toxic brain damage. High concentrations of unconjugated bilirubin suppress activity of mitochondrial enzymes in the neurons in the CNS, inhibit DNA replication and alter DNA structure and impair synthesis and posttranslational modifications of proteins in these cells. Moreover, unconjugated bilirubin in high concentrations alter tyrosine reuptake. Tyrosine normally participates in the transmission of nerve impulses. High concentrations of unconjugated bilirubin also suppress NMDA-receptors (receptors to the N-methyl-D-aspartate), which results in disturbance of neurons excitation and impulses transmission. At last, this bilirubin affects water and electrolyte transport in the renal tubules thus predisposing to

the volume overload and brain edema. In addition, high concentrations of unconjugated bilirubin impair neuronal glucose metabolism. All above-mentioned mechanisms are involved in the pathogenesis of the bilirubin encephalopathy. Differentiating neurons are most susceptible to unconjugated hyperbilirubinemia. Accumulation of bilirubin in the basal ganglia is caused kernicterus. It manifests by hypotonia, stupor, fever, seizures and extrapyramidal abnormalities initially with muscular hypertonia, delayed motor skills, and sensorineural hearing loss in the future. Some infants develop brain edema. Children with severe neonatal hyperbilirubinemia, especially boys, have lower IQ than healthy children. Different factors are able to potentiate bilirubin toxicity in affected infants: (1) hypoalbuminemia, which facilitates bilirubin passage through the blood-brain barrier; (2) increased permeability of the blood-brain barrier in some infectious diseases, acidosis, hyperoxic hypoxia, and sepsis and plasma hyperosmolarity.

Gilbert's disease incidence in general population varies from the 5 to 10%. Type of inheritance of such heterogeneous genetic disorder including gene mutations encoding UDP-glucuroniltransferase is autosomal-dominant. Besides this defect, uptake of unconjugated bilirubin by hepatocytes may be detected. Gilbert's disease is thought as a benign unconjugated hyperbilirubinemia, because of some patients have slightly elevation of unconjugated bilirubin in the blood serum and they have no any significant clinical symptoms. However, infectious diseases, toxic substances and some drugs provoke excessive hemolysis with appearance of jaundice.

Crigler-Najjar syndrome is a hereditary autosomal-recessive disorder, which is characterized by deficiency of the UDP-glucuroniltransferase. Crigler-Najjar syndrome Type I is resulted from the absence of this enzyme activity in hepatocytes with severe congenital jaundice and a gross form of bilirubin encephalopathy. Expectancy life duration of affected infants is not more than 15 months usually. Administration of the phenobarbital can't reduce unconjugated bilirubin level due to absence of the enzyme UDP-glucuroniltransferase. Crigler-Najjar syndrome Type II is resulted from the moderate decrease of the UDP-glucuroniltransferase activity with more benign outcomes. Phenobarbital is able to stimulate activity of the enzyme and to reduce unconjugated hyperbilirubinemia. That is why bilirubin encephalopathy is rare in affected infants.

Jaundice with predominant conjugated hyperbilirubinemia is caused by:

1. Impaired bile excretion in the bile ducts due to:
    - Hepatocellular injury in viral or toxic hepatitis and liver cirrhosis;
    - Bile congestion in the bile capillaries during intrahepatic cholestasis;
    - Hereditary defects of conjugated bilirubin transport from hepatocytes in the bile capillaries (Dubin-Johnson syndrome, Rotor's syndrome)
2. Damage of the intrahepatic bile ducts following:
    - Primary biliary liver cirrhosis;

- Primary sclerosing cholangitis;
- Neoplasms affecting liver;
- Graft rejection after liver transplantation;
- Functional bile cholestasis during pregnancy;
- Hereditary diseases with intrahepatic cholestasis.

3. Obstruction of extrahepatic bile-excreting ducts in:
   - Choledocholithiasis and cholelithiasis (obstruction by gallstones);
   - Neoplasms originated from bile-excreting ducts or head of pancreas or edema of the pancreas;
   - Stricture of extrahepatic bile ducts;
   - Obstruction of extrahepatic bile ducts with helminthes;
   - Primary sclerosing cholangitis.

During hepatocellular diseases (hepatitis, liver cirrhosis, and acute liver dystrophy) conjugated hyperbilirubinemia is a result of damage of hepatocytes architectonics which impairs excretion of conjugated bilirubin in the bile ducts. However, concentration of unconjugated bilirubin also rises in such pathologies due to poor conjugation of bilirubin with glucuronic acid.

Dubin-Johnson syndrome (chronic idiopathic jaundice) is caused by an impaired conjugated bilirubin and some metabolites of xenobiotic excretion from the hepatocytes in the bile ducts. Such genetic disorder with autosomal-recessive type of inheritance is a consequence of inactivating mutation of MRP2 gene. Abnormal MRP2 protein is unable to carry conjugated bilirubin in the bile ducts. This syndrome often doesn't lead to any clinical symptoms, but morphologically both microscopically and microscopically abnormalities in the liver are detected. Hepatocytes and Kupffer cells contain dark brown pigment in affected patients.

Rotor's syndrome (familial conjugated hyperbilirubinemia) with autosomal-recessive type of inheritance is similar to Dubin-Johnson syndrome, but in contrast to the latter, liver histology is normal.

Some hereditary diseases with intrahepatic cholestasis were described.

Byler's disease is manifested by progressing intrahepatic cholestasis, diarrhea and exocrine pancreatic insufficiency with progress into liver failure. The disease is similar to the progressive familial intrahepatic cholestasis. These pathologies and malignant recurrent intrahepatic cholestasis are resulted from mutation of FIC1 gene (**F**amilial **I**ntrahepatic **C**holestasis). Mutations of other genes (encoding transporter protein for bile salts and bilirubin in the biliary ducts, or protein transporter of phospholipids in the bile ducts) are also involved in the pathogenesis of hereditary intrahepatic cholestasis.

When type of hyperbilirubinemia is detected, it is necessary to reveal its underlying cause and to analyze concentration of bilirubin and its metabolites in the blood, urine and feces (Table 5-2).

Table 5-2. Clinical and laboratory findings in patients with different types of jaundice (R.K. Murray, 1998, with add-ins)

Type of jaundice	Colour of skin	Blood	Urine	Feces
Hemolytic	Lemon-yellow	Total bilirubin ↑; Unconjugated bilirubin ↑	Urobilinogen ↑; Bilirubin (-)	Stercobilin ↑; Dark stool
Hepatic	Saffron-yellow	Total bilirubin↑; Conjugated and unconjugated bilirubin ↑	Urobilinogen ↓; Bilirubin (+)	Stercobolin ↓; Light stool
Obstructive	Green-yellow	Total bilirubin↑ ; Conjugated bilirubin ↑	Urobilinogen (-); Bilirubin (+)	Stercobilin (-) or ↓↓↓; Colorless stool

↑ - concentration is increased; (+) - is detected; (-) – is not detected; ↓ - concentration is decreased; ↓↓↓ is detected in trace amounts.

Pathophysiologic basis for the management of jaundice: (1) detection of its causes and mechanisms; (2) treatment of underlying disorder – management of hepatocellular diseases, hemolytic anemia or causes of bile flow obstruction. In newborns to decrease concentration of unconjugated bilirubin it is necessary to use phototherapy and to administer low doses of phenobarbital. Phototherapy (placement of affected infant under special blue lighting lamp with wave length approximately 450 nm) is based on the ability of yellow pigment bilirubin to absorb blue light with its conversion in the water-soluble pigment lumirubin. Lumirubin is excreted with urine thus attenuating toxic effects of lipids-soluble unconjugated bilirubin on the brain. Phenobarbital activated UDP-glucuroniltransferase, which converts unconjugated bilirubin to its water-soluble conjugative form.

To treat obstructive jaundice it is rationale to restore normal bile outflow with conservative or surgical methods. If such treatment is impossible, symptomatic treatment of cholestatic syndrome is recommended.

Cholestatic syndrome

Intrahepatic or most commonly, extrahepatic cholestasis (See above-mentioned etiology) results in the cholestatic syndrome manifesting as following symptoms (Table 5-3):

Table 5-3. Clinical and laboratory features of the cholestatic syndrome

Symptoms	Pathogenesis
Jaundice with conjugated hyperbilirubinemia	Obturation of bile ducts → rise in intraductal pressure of the bile → increase of bile ducts permeability and/or their rupture → conjugated hyperbilirubinemia, cholemia
Pruritus	Deposition of bile salts in the skin → irritation of nerve endings or, alternatively pruritus in cholestatic syndrome may be explained by abnormal metabolism of endogenous opioids
Malabsorption and steatorrhea	Bile ducts obstruction → failure to emulsify fats and fat-soluble substances in the intestine → steatorrhea, malabsorption (See Table 4-5), deficiency of fat-soluble vitamins A, D, E, K
Disorders of lipid metabolism	Decreased lipid clearance via bile → hyperlipidemia, subcutaneous deposition of cholesterol with formation of xanthomas
Bleeding syndrome	Defects of vascular wall induced by cholemia; impairment of synthesis of vitamin-K-dependent clotting factors II, VII, IX and X; bile-salts induced acquired thrombocytopathia; development of coagulopathy in DIC complicated liver diseases
Arterial hypotension, bradycardia	Bile salts induced peripheral vasodilation; direct influence of bile salts on the sinus node
Neurological disorders (fatigue, weakness, insomnia, deferred response)	Toxic action of bile salts on neurons in the CNS; delayed neuromuscular transmission
Damage of hepatocytes	Induced by bile salts
Laboratory marks of cholestasis	Cholestasis affect basolateral membrane of hepatocytes and related enzymes with elevation activity of the alkaline phosphatase, ALT and AST

Hepatocellular diseases

Hepatocellular diseases include hepatosis, hepatitis and liver cirrhosis.

Hepatitis is an inflammatory liver disease with hepatocytes damage. It can be acute (lasting up to 6 months) or chronic (lasting more than 6 months), infectious and non-infectious. Etiology of hepatitis is following:

- Viruses of hepatitis A (HAV), B (HBV), C (HCV), D (HDV), E (HEV) and other viruses, such as Epstein-Barr virus, Ebola virus, rubella virus, herpes simplex virus, enteroviruses, etc.;
- Other microorganisms (Leptospira) and protozoa (Entamoeba histolytica), etc.;
- Toxins, venoms or drugs (acetaminophen, ethanol, gold salts, isoniazid, halothane, etc.);
- Liver ischemia, for instance, in advanced stage of any shock (so-called "Shock liver").

Pathophysiology of selected viral hepatitis

Hepatitis A virus is a small RNA enterovirus from the family of picornavirus with fecal-oral pathway of transmission. HAV may be detected at challenging dose in water, food, feces and contaminated pools. Incubation period lasts from 3 to 6 weeks with absence of any clinical signs of disease despite replication of virus and initial damage of hepatocytes. At appearance of clinical symptoms of disease patient becomes seropositive, and anti-HAV antibodies (IgM and IgG) can be detected. Replicated HAV directly damage hepatocytes, but some portion of hepatocytes dying due to direct cytotoxicity of lymphocytes and NK-cells (as a kind of hypersensitivity reaction type II). Damage of hepatocytes associates with elevation ALT level, because of the enzyme is located normally in the cytoplasm of hepatocytes. Particular features of hepatitis A are: (1) absence of virus carrying state after recovery; (2) immunity for life after recovery; (3) predomination of jaundice-free forms of disease; (4) low risk of fulminant hepatitis.

Hepatitis B virus is a DNA-containing virus from the family of hepadnavirus that is transmitted parenterally (by sexual contact or after contact with contaminated blood). Viral nucleus contains enzyme DNA-polymerase and has superficial antigen (HBsAg) with highest immunogenicity and nuclear antigens (HBcAg, HBeAg and HBxAg). HBV usually presents in the blood, saliva and sperm in high concentration. Incubation period lasts 4-14 weeks (commonly 8-12 weeks). Hepatitis B may elapse as acute, fulminant form progressing into lightning speed liver failure, chronic hepatitis or persistent asymptomatic carrying state. It seems to be likely that HBV doesn't kill hepatocytes directly. Replication of virus leads to expression of HBsAg and other proteins on the surface of virion. Such components are recognized by antigen presenting cells, namely, by Kupffer macrophages. After that processed peptides in complex with MHC molecules class I or II are presented to CD8+ or CD4+ lymphocytes, accordingly. CD8+ cells directly damage hepatocytes by released from them proinflammatory cytokines IFN-γ and TNF-α, ROS, RNS, and proteases. Besides that, IFN-γ and TNF-α suppress viral replication in

hepatocytes. CD4+ cells are able to activate CD8+. Hepatocytes injury is manifested by the appearance of specific hepatic enzymes in the blood. Detection of such enzymes, viral antigens and antibodies against viral antigens helps to understand severity and stage of disease. For instance, HBeAg is a marker of infectivity; HBsAg, which is determined following 1-2 weeks after contamination, demonstrates active viral gene expression; anti-HBsAg, anti-HBcAg and anti-HBeAg are late antibodies which are detected even after recovery; however, lifelong immunity after recovery is achieved mainly by ant-HBsAg. Excessive formation of antibodies may lead to the formation of immune complexes (for example, HBsAg-anti-HBsAg), which after deposition in the vascular walls, joints, kidneys glomeruli, etc. participate in the hypersensitivity reactions type III with development of vasculitis, urticaria, arthritis, pancreatitis, glomerulonephritis, and cryoglobulinemia. Particular features of hepatitis B include: (1) chance of acute fulminant hepatitis is approximately 2%; (2) development of chronic hepatitis in 5-10% of patients; (3) increased risk of hepatic carcinoma development, especially among HBeAg carriers.

Hepatitis C virus is RNA virus from the family of flavivirus with parenteral pathway of transmission (including sexual contacts and transplacental transfer). Hepatitis C was termed “non-A, non-B hepatitis” formerly. Patients with regularly transfusions of blood have greatest risk for HCV infection. After infection incubation period continues 2-25 weeks (7-8 weeks usually). After replication HCV expresses superficial viral coat protein E_2, which selectively binds with CD81 (protein tetraspanin) expressed by hepatocytes and B-cells. HCV directly affects hepatocytes and activate T-helper cells and cytotoxic T-cells which also damage hepatocytes. Particular features of hepatitis C are: (1) silent acute inflammation; (2) fulminant hepatitis develops rare; (3) transformation into chronic hepatitis in most infected patients; (4) high risk of liver cirrhosis development and it transformation in the liver cancer. These facts explain why HCV was termed colorfully as a “sweet killer”. HCV also replicate in the lymphoid cells thus leading to autoimmunity and lymphoproliferative disorders. Deposition of immune complexes in the vasculature, joints and skin results in vasculitis, glomerulonephritis, arthritis, and dermatitis. Non-Hodgkin’s lymphomas may develop in patients with hepatitis C.

Hepatitis D virus (delta) is RNA virus that requires presence of HBV to cause inflammation in the liver. Hepatitis D may develop as coinfection (after simultaneous infection with HDV and HBV) or superinfection (if infection of HDV occurs after infection with HBV). After parenteral route of transmission incubation period lasts from 4 to 26 weeks (upon average 10 weeks). Superinfection is characterized by fulminant liver failure in 70-90% of infected patient, whereas during coinfection its risk is lower usually. Superinfection also may lead to chronic hepatitis. Hepatic carcinoma is relatively common outcome of hepatitis D.

Hepatitis E virus is RNA virus belonging to the calicivirus family with fecal-to-oral pathway of transmission. Incubation period length varies from 2 to 9 weeks (5-6 weeks usually). HEV most commonly affects patients in developing

countries of Africa and Asia. Hepatitis E is acute infection, which may be potentially life-threatening to pregnant females due to development of fulminant liver failure. Chronic hepatitis and hepatic carcinoma are uncommon.

Drug-induced liver disease

Liver plays an important role in the development of detoxification of almost all xenobiotics that is why drug-induced liver disease is relatively common. During metabolic conversion lipophilic xenobiotics become more hydrophilic with subsequent their excretion from the organism with bile or urine. Oxidative reactions catalyzed by enzymes of P-450 cytochromes family are thought to be main detoxifying enzymes. Then oxidized metabolites conjugate or with glucuronic acid, or with sulfuric acid, or with reduced glutathione, bind with transporter proteins and excrete from hepatocytes in the blood or in the bile.

Drug-induced hepatotoxic reactions are classified into acute and chronic; idiosyncratic and dose-dependent. Severity of drug-induced hepatotoxic reactions depends on the certain factors:

- Type of drug and particular features of its metabolism;
- Dose of drug;
- Patient's age, sex and body mass index;
- Underlying diseases of the liver and kidneys, pregnancy;
- Genetic predisposition (determining activity of xenobiotic metabolizing liver enzymes).

Drug-induced hepatotoxic reactions are manifested by laboratory signs of hepatocytes injury (by increased activity of definite enzymes in the blood serum, See below), cholestatic syndrome and jaundice, and clinical signs of liver failure.

Idiosyncratic reactions have latent period lasting 5-90 days and in case of ongoing use of drug may be potentially lethal. As a rule, idiosyncratic reactions are dose-independent. They may be caused by different drugs. There are several mechanisms of idiosyncratic drug-induced hepatotoxic reactions:

1. Metabolites of some drugs (isoniazid, diclofenac, lovastatin and some other drugs) after oxidative modification by cytochrome P-450 enzymes covalently bind with intracellular and membrane proteins with subsequent ATP deficiency, ionic disbalance of hepatocytes, disruption of their cytoskeleton and osmotic swelling and lysis.
2. Some drugs or their metabolites may bind with hepatic transporter proteins or proteins of bile ducts with development of intrahepatic cholestasis. Intrahepatic cholestasis as a side effect is common to estrogens, androgens, anabolic steroids, antibiotics erythromycins, rifampin, antipsychotic drug amitriptyline, benzodiazepine diazepam and some others. Pregnant female with mutations or polymorphisms of MRP3 protein may develop intrahepatic

cholestasis associated with hyperestrogenic state during pregnancy. Intrahepatic cholestasis may cause secondary injury of hepatocytes.

3. Cytochrome P-450-mediated oxidation of some drugs results formation of metabolites which are able to bind covalently with these and other enzymes with formation of adducts with antigenic properties. As a result, activity of such enzyme reduces and immune cells may damage hepatocytes. After transportation of enzyme-metabolite complexes in specific vesicles to the cellular membranes such complexes are recognized by APCs and attacked by cytotoxic T-cells with secondary injury and inflammation. Proinflammatory cytokines deepen injury of hepatocytes and they die from necrosis and/or apoptosis. Such side effects possess nitrofuranes, methyldopa, lovastatin, and antibiotic minocycline. Moreover, metabolites of halothane, phenytoin and sulfamethoxazole activate Th2 cells and plasma cells with synthesis of IgE in high amounts, IgE-driven degranulation of mast cells and hepatocytes injury by mediators of allergy and inflammation.
4. Some drug metabolites are able to stimulate of proapoptotic receptors on the membrane of hepatocytes with subsequent Fas- or TNF-α-mediated extrinsic pathway of apoptosis. Expression of prosurvival molecules, in contrast, is reduced.
5. Inhibitors of viral reverse transcriptase, sodium valproate, tetracyclines, aspirin and other drugs after their metabolism can damage mitochondria of hepatocytes by binding with enzymes of respiratory chain or mitochondrial DNA. Such action causes oxidative and nitrozative stress in hepatocytes, disruption of oxidative phosphorylation, accumulation of lactate and triglycerides in affected cells, which dying due to necrosis and inflammation.
6. Some drugs for chemotherapy of neoplasms (cytosine, daunorubicine) affect endothelial cells of hepatic sinusoids with development of vascular (venoocclusive) liver injury.
7. Diltiazem, quinidine and sulfur-containing drugs activate Kupffer and stellate cells producing growth factors and cytokines, which stimulate fibroblasts to synthetize of extracellular matrix components. As a result, granulomatous inflammation in the liver occurring.
8. Continuous use of hormonal estrogen- or androgen-containing drugs may impair hepatocytes differentiation with development of benign adenomas of the liver or rare – liver adenocarcinoma.
9. Most drugs and/or their metabolites usually provoke hepatotoxic reactions by several mechanisms.

Dose-dependent hepatotoxic reactions are caused most commonly by acetaminophen (paracetamol), amiodarone, cyclophosphamide, methotrexate, niacin and oral contraceptives. Up to 40% of all dose-dependent hepatotoxic reactions are induced by acetaminophen, which is used traditionally as an antipyretic and analgesic drug with minimal anti-inflammatory action. After ingestion, at least 90% of

acetaminophen is conjugated with glucuronic acid or sulfuric acid in hepatocytes with formation of non-toxic metabolites excreted with urine. Residuary parts of metabolites are oxidized by P-450 cytochromes with formation of highly reactive and potentially toxic nucleophilic N-acetyl-parabenzoquinone-imine. If acetaminophen was received in therapeutic dose, such metabolite after interaction with reduced glutathione is inactivated and excreted with urine. However, in case of acetaminophen overdose (250 mg/kg and higher) contribution of P-450 cytochromes-mediated detoxification rises significantly with astonishing of reduced glutathione (GSH) pool. On the one hand, it promotes toxic effects of the N-acetyl-parabenzoquinone-imine; on the other hand, it leads to abnormal ratio between reduced and oxidized glutathione (GSH/GSSG) with a disorder of hepatocytes redox state, their dysfunction and hepatocytes death from necrosis or apoptosis. That is why acetaminophen-induced liver injury is treated by thiol-containing antioxidant with low molecular weight N-acetyl-L-cysteine, a precursor of reduced glutathione.

Alcoholic liver disease

Chronic alcohol abuse induces liver disease including:

- Alcoholic steatosis;
- Alcoholic hepatitis;
- Liver cirrhosis;
- Adenocarcinoma of the liver.

Regularly consumption of 80 g of ethanol per day is sufficient to produce alcohol-induced liver disease in males, whereas daily consumption of 20 g of ethanol during one year leads to such pathology in females. Liver cirrhosis affects at least 15% of alcoholics, and liver cirrhosis developing following approximately 10 years of alcohol abuse. Natural history of alcohol-induced liver disease depends on genetic predisposition (for instance, polymorphism of genes encoding ethanol-metabolizing enzymes), and coexisting pathologies affecting liver (obesity, hepatitis C infection, use of hepatotoxic substances). The fact of relatively common prevalence of alcohol-induced liver diseases is explained by the following: at least of 90-95% of ingested alcohol is metabolized to the acetaldehyde and acetate in the liver and only 5-10% of ethanol is excreted in unchanged form. Basic ethanol-metabolizing enzymes are cytosolic NAD^+-dependent alcohol dehydrogenase, microsomal NADPH-dependent ethanol-oxidizing system and catalase. In chronic alcohol abusers role of two later enzymes is significantly higher, and if in normal individual liver degrades 7-10 g of ethanol per hour, in alcoholic degradation rate of alcohol is greater.

Pathogenesis of alcohol-induced steatosis (fatty degeneration of the liver) can be explained as following:

(1) Ethanol stimulates release of epinephrine and ACTH, which stimulate lipolysis. As a result, transport of fatty acids in hepatocytes increases.

(2) Ethanol induces synthesis of fatty acids in the liver and inhibits their β-oxidation; augments triglycerides synthesis and impairs release of lipoproteins in the blood. Lipids deposit in the centrilobular area initially with progression of lipid droplets deposition. Accumulation of fats in hepatocytes is a complex process, which is determined by switching of multiply metabolic pathways: blockade of PPARα and of adenosine monophosphate-activated protein kinase (AMPK), which is responsible for fatty acid oxidation; sterol regulatory element-binding protein 1c (SREBP1c) activation, which is responsible for fatty acid synthesis; endoplasmic reticulum stress (See below); decreased production of protective adipokine adiponectin during chronic inflammation. Other metabolic pathways (activation of histone deacetylase sirtuin-1, cannabinoid receptors, complement system and PPAR-γ alongside with insulin resistance might also amplify alcoholic steatosis. Steatosis is a potentially reversible disorder and alcohol cessation may reverse fat dystrophy. No any clinical signs can be detected during alcohol-induced fatty hepatosis. However, it is important to remember that fatty hepatosis is a frequent hallmark of some pathologies including obesity, decompensated diabetes mellitus, severe protein malnutrition and prolonged use of corticosteroid drugs.

Alcohol-induced hepatitis is characterized by central necrosis of hepatocytes, infiltration of damaged tissue with neutrophils, and fibrosis. Mechanisms of hepatitis development include:

(1) Ethanol impairs cellular respiration of hepatocytes with hyperproduction of ROS in the mitochondria, which reduces intracellular pool of GSH with development of oxidative stress. It leads to membrane damage, damage of lipids, proteins and nucleic acids and ATP depletion. As a result, hepatocytes swell and die from necrosis.

(2) Ethanol directly damage hepatocytes with releasing from dying cells DAMPs with development of sterile inflammation, fibrogenesis and regeneration.

(3) Chronic alcohol abuse increases intestinal permeability with pronounced enteral bacterial translocation. Destruction of Gram-negative microbes with releasing of endotoxin results in the infectious inflammation and overproduction of proinflammatory cytokines TNF-α, IL-1, IL-6, and IL-8. They stimulate inflammation, necrosis or apoptosis of hepatocytes.

(4) Chronic intoxication with alcohol depletes concentration of reduced glutathione thus impairing redox state and leading to more severe oxidative-mediated hepatocytes injury.

(5) Endoplasmic reticulum stress is a meaningful pathogenetic mechanism of alcoholic liver disease. The endoplasmic reticulum is an important organelle for the folding of proteins. Impairment of proteins folding results in accumulation of unfolded proteins in the endoplas-

mic reticulum that activate several pathways leading to endoplasmic reticulum stress. It supports inflammation in the liver, causes apoptotic death of hepatocytes, impairs calcium homeostasis in these cells, and provokes steatogenic response. Ethanol also triggers endoplasmic reticulum stress in the stellate cells with their activation and fibrogenesis.

Alcoholic hepatitis is confirmed by laboratory marks of hepatocellular damage (See below).

Alcoholic liver cirrhosis is a natural outcome of alcoholic liver disease. Histologically it is characterized by pericentral necrosis of hepatocytes, accumulation of hyaline (Mallory bodies) and fibrosis of parenchyma. Fibrosis is caused by disbalance between formation and degradation of extracellular matrix components. Collagen fibers are formed by stellate cells and fibroblasts after their stimulation by growth factors (TGF-β, PDGF, FGF) produced by activated hepatocytes, leukocytes, endothelial cells, etc. Excessive fibrogenesis is a part of inflammation resolution program, but despite this fact, it impairs blood flow in the portal vein which leads to appearance of nodes of hepatocytes regeneration and portosystemic shunting of the blood. Alcoholic liver cirrhosis manifests by clinical signs of liver failure, hepatorenal syndrome and portal hypertension.

Hepatic adenocarcinoma may develop in patients with alcoholic liver cirrhosis. It is due to damage of genetic material of hepatocytes and impairment their cell cycle.

Pathophysiologic basis for the treatment of alcoholic liver disease include: (1) cessation of alcohol intake; (2) nutritional support; (3) modulation of inflammation and fibrogenesis with corticosteroids, anticytokine therapy and xanthine pentoxiphylline; (4) management of oxidative stress with a precursor of glutathione S-adenosylmethionine; (5) reduction of endoplasmic reticulum stress with betaine; (6) poor absorbable antibiotics to control bacterial overgrowth and bacterial translocation; (7) probiotics and prebiotics; (8) colony stimulating factors and/or stem cells to stimulate regeneration of hepatocytes.

Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is thought now to be as a part of metabolic syndrome affecting up to one third of population in developed countries. To better understanding pathogenesis of NAFLD is strongly recommended to reread information about obesity and metabolic syndrome (Part XI “Nutritional disorders” in the Textbook “General pathophysiology: the essentials”). Natural history of NAFLD is illustrated in the Fig. 5-3.

Excessive concentrations of FFAs (of dietary origin and due to excessive lipolysis in insulin-resistant individuals) accumulate in adipocytes as triglycerides and some lipid metabolites including diacylglycerol. Excretion of FFAs in the form of VLDL in insulin-resistant individuals is reduced. In turn, FFAs potentiates insulin resistance. Some, especially saturated FFAs are able to induce oxidative stress

and endoplasmic reticulum stress and trigger inflammasome activation. Saturated fatty acids are also substrates for lipotoxic ceramides for the liver and pancreas.

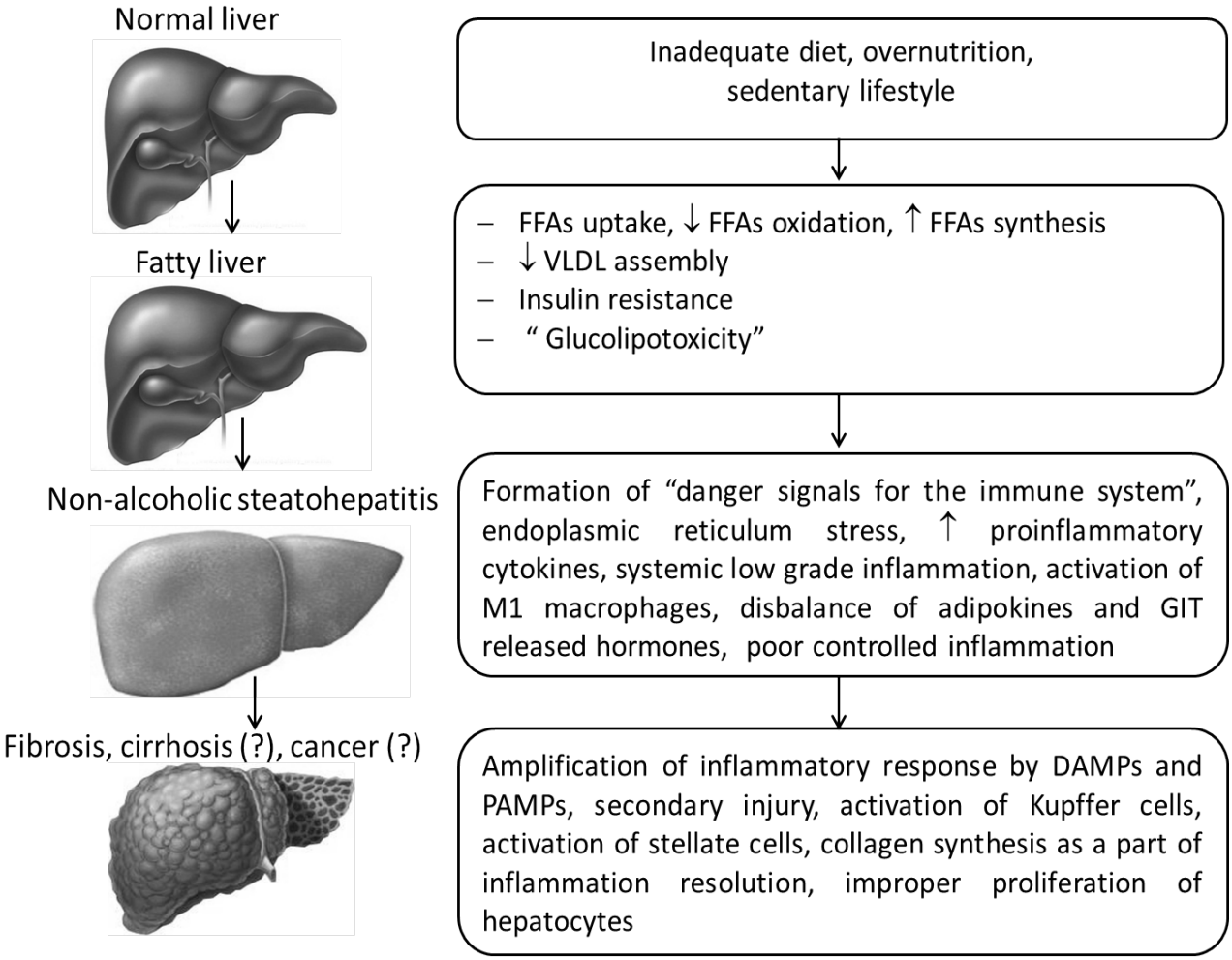


Figure 5-3. Simplified pathogenesis of NAFLD

DAMPs, Damage Associated Molecular Patterns; FFAs, Free Fatty Acids; GIT, Gastrointestinal tract; M1, Macrophages with proinflammatory phenotype; PAMPS, Pathogen Associated Molecular Patterns; VLDL, Very Low Density Lipoproteins

Insulin resistance, "glucolipotoxicity" trigger proinflammatory signalling pathways. Systemic low grade inflammation is supported by disbalance of biologically active substances produced in the gastrointestinal tract, adipose tissue and skeletal muscles. So, deficiency of "protective" adipokine adiponectin, hyperleptinemia, increase concentration of glucagon, lack of secretion and/or action of gut-derived Glucagon-Like Peptide (GLP-1) and ghrelin released from the stomach and duodenum are important "players" of inflammation in NAFLD. Polarizations of immune response with predomination of classically activated macrophages (M1), increase of intestinal permeability, dysbiosis, and secondary infectious and non-infectious diseases (with recognition of both PAMPs and DAMPs by antigen presenting cells) support and reinforce steatohepatitis. Kupffer cells activate stellate cells with

subsequent synthesis of collagen and liver fibrosis. In some cases, NAFLD may progress into liver cirrhosis and liver carcinoma.

Assessment of laboratory tests indicating liver pathology

Hepatocytes contain thousands of enzymes and elevation activity of some of them is strongly associated with hepatocellular or cholestatic liver diseases. That is why such enzymes are called as indicated. Some of these enzymes are located in the cytoplasm of hepatocytes (aminotransferases ALT, AST, lactate dehydrogenase LDH), others are conserved or in the mitochondria (malate dehydrogenase MDH, glutamate dehydrogenase GDH), or in the endoplasmic reticulum (different hydroxylases, acetylases, glucuroniltransferases), or in the ribosomes (cholinesterase) or in the lysosomes (hydrolases). Some hepatocellular enzymes are bounded with membranes. For instance, γ-glutamyl transpeptidase (γ-GTP), 5-nucleotidase, alkaline phosphatase and leucin aminopeptidase are linked with canalicular membrane of hepatocytes (membrane in close proximity to the bile capillaries).

Interpretation of excessive activity of some these enzymes are summarized below. To assessment origin of liver diseases, Table 5-4 is useful.

Table 5-4. Interpretation of elevated serum activity of enzymes during liver pathology

Hepatocellular diseases	**Diseases with cholestatic syndrome**
↑↑↑ activity: ALT, AST, LDH_5, MDH, GDH ↑ activity: alkaline phosphatase, γ-GTP, 5-nucleotidase, leucine aminopeptidase	↑↑↑ activity: alkaline phosphatase, γ-GTP, 5-nucleotidase, leucine aminopeptidase ↑ activity: ALT, AST, LDH_5, MDH, GDH

Excessive activity of amino transferases. Physiologically, AST and ALT are widely distributed in different tissues and organs. AST are detected in the cells of the liver, myocardium, skeletal muscles, kidneys, brain, pancreas, lungs, red blood cells and leukocytes. The highest concentration of ALT is determined in hepatocytes. Release of AST and ALT in the blood from damaged hepatocytes or due to increased membrane permeability or due to irreversible injury of hepatocytes demonstrates loss of hepatocellular membranes integrity and can't help to distinguish potentially reversible damage of hepatocytes from irreversible. As a rule, excessive activity of AST and, especially, ALT in the blood is due to acute and chronic hepatitis with infectious and non-infectious etiology, alcoholic liver disease, non-alcoholic liver steatosis, and liver cirrhosis complicated hemochromatosis, Wilson's disease and α_1-antitrypsin deficiency. However, AST and ALT are

not strictly specific for hepatocellular injury. Several causes of such hyperenzymemia unrelated to the liver damage were documented including hereditary metabolic disorders in the skeletal muscles, acquired diseases of skeletal muscles, excessive physical activity and celiac disease. Prolonged use of some drugs (synthetic penicillines, ciprofloxacin, nitrofuranes, isoniazid, some antifungals, antiepileptics NSAIDs, HMG-KoA reductase inhibitors, steroid anabolics and others) may provoke excessive activity of both AST and ALT. Some particular features of amino transferases elevation in some liver diseases were described. Thus, ratio AST/ALT is 2 or more in alcoholic liver disease, because alcohol overconsumption leads to deficiency of pyridoxal-5-phosphate and decrease activity of the ALT. If ratio AST/ALT is less than 1, viral hepatitis or extrahepatic obstruction of bile ducts should be suspected. In such circumstances, low AST/ALT ratio is caused by releasing of ALT from hepatocytes in the blood.

Excessive activity of lactate dehydrogenase (LDH)**.** Because of presence of such enzyme in the cytoplasm of different cells including cardiomyocytes, skeletal muscles, lungs, blood cells, not only hepatocytes, one should consider elevation activity of namely LDH_5 as a marker of hepatocellular damage.

Excessive activity of malate dehydrogenase (MDH) and glutamate dehydrogenase (GDH) reflects mitochondrial damage in hepatocytes. Elevation of GDH activity is an early laboratory marker of alcoholic liver injury. Metabolic conversion of ethanol in mitochondria of hepatocytes leads to mitochondrial swelling, damage of internal mitochondrial membrane, impairment of cellular respiration, oxidative and nitrozative stress with subsequent destruction of mitochondria.

Elevated alkaline phosphatase activity may be physiological and pathological. In physiological conditions excessive activity of alkaline phosphatase is detected during 3rd trimester of pregnancy due to releasing of placental alkaline phosphatase in the blood. Sometimes consumption of fatty food by persons having of the (0) or (B) blood group stimulates releasing of intestinal alkaline phosphatase in the blood. Activity of the enzyme rises usually in teenagers during their accelerated growth and females at the age of 40-65 years due to release of alkaline phosphatase from bones indicating initial stage of osteoporosis.

Pathological elevated activity of alkaline phosphatase is explained by different diseases of the bones or by liver diseases. In last cases, elevated activity of alkaline phosphatase combines usually with elevated activity of other indicated enzymes. Elevated alkaline phosphatase activity is resulted from cholestatic liver injury (obstruction of bile ducts, primary biliary liver cirrhosis, sclerosing cholangitis, drug-induced cholestasis, etc.), infiltrative liver diseases (sarcoidosis, granulomatous diseases, metastatic damage of the liver). Detachment of the enzyme with canalicular membrane of hepatocytes and releasing in the blood is a leading cause of elevated serum alkaline phosphatase activity in these disorders.

Elevated serum γ-glutamyl transpeptidase (γ-GTP) activity is a relatively specific indicator of hepatobiliary diseases, namely cholestasis. Excessive activity of γ-GTP may be detected also in patients with acute or chronic alcohol-induced

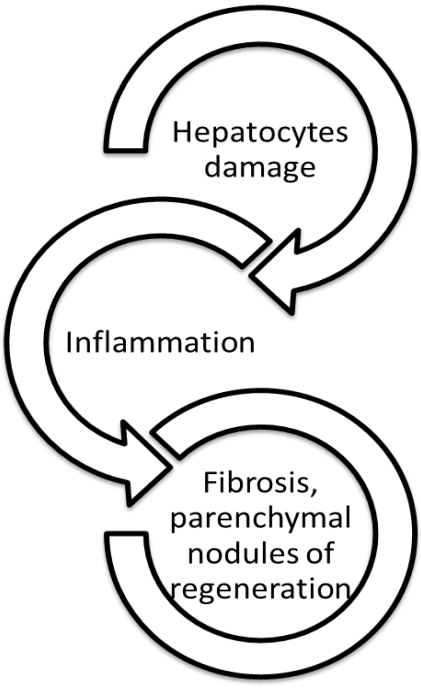
liver disease. Elevated activity of the enzyme during intrahepatic cholestasis is related to increased concentration of lipoproteins, "carriers" of this enzyme. Elevated activity of γ-GTP is documented also in patients with pancreatic diseases, myocardial infarction, renal failure, COPD, diabetes mellitus and use of some drugs (barbiturates, anticoagulants, steroid anabolics, synthetic estrogens and others).

Liver cirrhosis

The term "cirrhosis" was firstly proposed by Laennec as a translation from the Greek "scirrhus" (orange), because of liver surface becomes bumpy and dark orange. Liver cirrhosis is the end stage of different liver diseases which cause damage of liver parenchyma, with signs of inflammation and its resolution. Basically, liver cirrhosis is characterized by following features: (1) progressive parenchymal injury; (2) inflammation; (3) excessive deposition of extracellular matrix components (collagen, glycoproteins, proteoglycans) with development of potentially reversible fibrosis which bridges liver tissue; (4) formation of nodules of regenerating hepatocytes; (5) destruction of normal liver architecture.

Etiology of liver cirrhosis involves viral hepatitis B and C, chronic alcoholism, their combination, autoimmune hepatitis, autoimmune-mediated injury of bile ducts (primary biliary cirrhosis), sclerosing cholangitis, hemochromatosis, Wilson's disease, α_1-antitrypsin deficiency, granulomatous diseases, drug-induced liver injury, vascular diseases affecting liver, congestive heart failure, etc. Liver cirrhosis with unrecognized etiology is determined to be "cryptogenic".

Pathogenesis of liver cirrhosis is presented in the Fig. 5-4:



Damage of hepatocytes → inflammation → activation of stellate cells (Ito cells) by paracrine acting cytokines and growth factors released from hepatocytes, Kupffer cells, sinusoidal macrophages → formation of collagen fibers I, III and V types, glycoproteins and proteoglycans by stellate cells → deposition of extracellular matrix components in the perisinusoidal (Disse) space → gaining of "contractile" phenotype by stellate cells → rise in hydrostatic pressure in the portal vein → blood shunting in the liver → hypoxia of hepatocytes → fibrosis, nodules of hepatocytes regeneration → portal hypertension → liver failure, ascites, hepatorenal syndrome → polyorgan failure, death.

Figure 5-4.Simplified pathogenesis of liver cirrhosis

Portal hypertension during liver cirrhosis is caused by multiply mechanisms:

- Accumulation of extracellular matrix components in Disse space;
- Contraction of hepatic stellate cells and decrease of sinusoidal lumen;
- Rise of portal vessels resistance due to compression of venules by regeneration nodes and local hyperproduction of vasoconstrictors, for instance, endothelin-1;
- Overfilling of portal vein with blood, which is resulted from production in great amounts vasodilating substances (glucagon, VIP, substance P, prostacyclin, gasotransmitters) in arteries of internal organs in the abdominal cavity.

Depending on the etiology, liver cirrhosis has some particular pathogenetic features. Hence, liver cirrhosis complicated hemochromatosis is a result from severe oxidative stress, whereas accumulation of free redox-active iron initiates Fenton reaction with formation of potentially high-reactive and cytotoxic hydroxyl radical. Similar oxidative-mediated injury of the liver by copper-induced oxidative stress leads to liver cirrhosis in Wilson disease. However, cholestasis also may play a significant role in the pathogenesis of liver cirrhosis complicated hemochromatosis and Wilson disease. Patients with later hereditary disease develop cirrhosis early, even during their childhood. Liver cirrhosis in patients with α_1-antitrypsin deficiency, which is a hereditary disorder with autosomal recessive type of inheritance, often combines with pulmonary emphysema as a result of disbalance in the system proteases/inhibitors of proteases and cholestasis. Risk of hepatocellular carcinoma is relatively high.

Primary biliary cirrhosis is an endpoint of chronic autoimmune mediated injury of bile ducts for example, in primary sclerosing cholangitis. It affects predominantly females at age of 30-65 years old which usually have different autoimmune diseases. Autoantibodies against components of mitochondria, nuclei, receptors, ribonucleoproteins, etc. are detected in patient's serum. Immune complexes and self-reactive T-cells damage epithelial cells of bile ducts and activate complement system. As a result, chronic destructive cholangitis develops with pronounced cholestatic syndrome manifesting with excruciating skin itching. Different groups of drugs are widely used to treat primary biliary cirrhosis. Ursodeoxycholic acid reduces hydrophobicity of bile and modulates activity of dendritic cells. To suppress inflammation corticosteroids, cytotoxic drugs, and cyclosporine A are indicated. Farnesoid receptor agonists (obeticholic acid) are thought to be effective. Normally, farnesoid X receptor (FXR) in the liver reduces conversion of cholesterol to bile acids by downregulating the expression of enzymes involved in bile acid synthesis. FXR also reduces bile acid toxicity. Bile acids are conjugated to either glycine or taurine before secretion into the bile; FXR enhances bile acid conjugation with these substances and promotes the transport of bile acids to the gall bladder. Within the intestine, FXR reduces bile acid absorption, promotes bile acid movement across the enterocyte, and promotes recycling of bile acids to the liver. Moreover, FXR reduces hepatic uptake of bile acids, reduces gluconeogenesis and lipogene-

sis. So, FXR agonists have pleiotropic positive effects. Anti-CD20 monoclonal antibodies help to selectively deplete B-cells. Mesenchymal cells transplantation and liver transplantation are recommended in severe cases.

Cardiac liver cirrhosis is a relatively rare now and is developed in patients with right-sided heart failure. Blood congestion in vena cava inferior leads to passive hyperemia of the liver and it's enlargement. Hypoxia, centrilobular necrosis of hepatocytes stimulates inflammation and expansion of fibrosis.

Liver cirrhosis relates to different clinical and laboratory complications:

- Portal hypertension;
- Liver failure;
- Ascites;
- Hepatic encephalopathy;
- Jaundice;
- Hepatorenal syndrome;
- Hepatopulmonary syndrome;
- Elevated activity of specific liver enzymes (See Table 5-4);
- Anemia, thrombocytopenia, neutropenia, DIC or coagulopathy;
- Bleeding from varicose dilating veins;
- Spontaneous bacterial peritonitis;
- Bone disease;
- Liver cell carcinoma.

Pathophysiological basis for treatment of liver cirrhosis: (1) etiologic treatment meaning management of underlying disorder (for example, use of antiviral drugs in case of viral hepatitis, chelation of iron or copper during hemochromatosis or Wilson's disease, adequate treatment of heart failure, etc.); (2) pathogenetic therapy specific to each form of liver cirrhosis (See above); (3) avoidance of alcohol and hepatotoxic drugs and substances; (4) management of complications (See below); (5) stem cells therapy as a potentially new strategy; (6) liver transplantation.

Liver failure

Liver failure is a syndrome resulting from primary or secondary liver injury which is characterized by pronounced disorders of protein, lipid and carbohydrate metabolism, lack of detoxicative function and development of hepatic encephalopathy.

Liver failure can be classified into fulminant, acute, subacute and chronic. Conventionally, according with basic pathogenetic mechanism, hepatic coma is classified into "hepatocellular", which is caused by massive death of hepatocytes (following viral hepatitis, intoxications with toxic substances, drug-induced liver injury, abnormal blood flow during shock, etc.) and "portosystemic" liver failure. The latter is resulted from reorganization of liver architecture and portosystemic

shunting of the venous blood from the portal vein into hepatic veins without previous detoxification.

Different symptoms developing during liver failure:

1. Disorders of protein metabolism. Hepatocytes loss their ability to synthetize normal amounts of proteins, mainly albumins. Decrease in albumin concentration in the blood leads to decline of oncotic pressure which predisposes to edema and ascites formation. Diminished formation of clotting factors (fibrinogen, prothrombin, III, V, VII, IX, X and XI clotting factors) in hepatocytes leads to bleeding syndrome. Inadequate formation of transport proteins (haptoglobin, transferrin, ceruloplasmin, transport proteins for steroid hormones) provokes micronutrients deficiency, endocrine disorders and impairment of pharmacokinetics of some drugs.

2. Disorders of carbohydrate metabolism. Pool of glycogen in hepatocytes is astonished; gluconeogenesis is suppressed, partially due to inability of glucagon to stimulate this process. As a result, patients with liver cirrhosis may have hypoglycemia. Its severity may increase in case of portosystemic shunting of the blood, because of poor degradation of insulin by hepatocytes.

3. Disorders of lipid metabolism are characterized by abnormal concentration of cholesterol and lipoproteins in the blood serum.

4. Jaundice is a result of damage of hepatocytes and/or hepatocytes dysfunction. Both conjugated and unconjugated hyperbilirubinemia are laboratory markers of jaundice in patients with liver cirrhosis.

5. Disseminated Intravascular Coagulation. Pathogenetic mechanisms of such complication are following:

- Contact activation of factor XII by endotoxin and bile acids and endothelial dysfunction with loss of athrombogenic surface and TF-mediated stimulation of coagulation;
- Impairment of synthesis of coagulation factors and natural anticoagulants in the liver;
- Thrombocytopenia due to hypersplenism – spleen enlargement and sequestration of platelets and red blood cells in it; inadequate formation of platelets in the bone marrow during endogenous intoxication and platelets consumption during 1st stage of DIC;
- Thrombocytopathia.

6. Endocrine disorders mainly are caused by abnormal metabolic degradation of sex hormones. At normal circumstances, male steroid hormones are metabolized to estrogens in the liver. During hepatocellular failure insufficiency of such metabolic conversion is compensated by extrahepatic metabolism of androgens to estrogens in the skin, adipose tissue, muscles and bones. If hepatocellular failure coexists with portosystemic blood shunting, time of circulation of metabolites with estrogenic-like activity in the blood significantly increases in male patients. Hyperestrogenemia partially is also caused by poor production of sex-hormone bind-

ing globulin in the liver. Affected males demonstrate clinical signs of feminization like gynecomastia, decreased libido, impotence, testicular atrophy, loss of sexual hair distribution. Endocrine disorders in female patients are characterized by menstrual cycle disorders, uterine bleeding, subfertility or infertility.

7. Hepatorenal syndrome is a potentially reversible disorder of kidneys function during liver failure which is characterized by oliguria or anuria and azotemia. Minimal morphological changes are detected usually in kidneys, and liver transplantation helps to relive completely renal failure. Exact mechanism of hepatorenal syndrome is unknown; however, vasoconstriction of renal arteries due to disbalance of vasoconstrictors and vasodilators and abnormally low sodium reabsorption were proposed as significant pathogenetic mechanisms of hepatorenal syndrome.

8. Hepatopulmonary syndrome is caused by formation of arteriovenous anastomosis and corresponding blood shunting in the lungs due to disbalance between vasoconstrictors and vasodilators combined with alveolar hypoventilation and shift of oxy-Hb dissociation curve to the right with poorly understood mechanism of development.

9. Enteral endotoxinemia develops, when amounts of endotoxin in the blood absorbed from the intestine and gut exceeds ability of Kupffer cells to destroy it. Intensive growths of Gram-negative microorganisms in the intestine, and mainly, in the gut and high permeability of intestinal and colonic mucosa during liver failure are main mechanisms of such complication. Endotoxin activates Kupffer cells, neutrophils, macrophages, endothelial cells, hepatocytes to produce proinflammatory cytokines. Complement activation produces more pronounced activation of these cells and secondary injury of hepatocytes. Moreover, endotoxin activates platelets and endothelial cells with microvascular thrombosis in the liver and more severe hypoxic injury of hepatocytes. As a result, hepatocytes dye from necrosis and apoptosis. Enteral endotoxinemia also is a leading mechanism of hepatic encephalopathy during liver failure.

10. Hepatic encephalopathy is a progressing disorder of brain functions following liver failure. During initial stage only slightly slowed mental reactions are detected; poor memory, emotional instability and sleep disorders (sleeplessness at night and sleepiness at day time) develop more slowly. During next precoma stage, patient becomes disoriented and sometimes aggressive, flapping tremor (asterixis) may appear, reflexes decrease. Hepatic coma requires intensive therapy. It is characterized by absence of any response to external stimuli, “hepatic smell” from the mouth and seizures.

Hepatic encephalopathy is a result of a net of mechanisms:

- Action of neurotoxic substances (ammonia, phenols, thiols and short chain fatty acids) on neurons in the CNS. Ammonia plays a central role in this process. It is produced from proteins in the gut under action of bacterial urease. Significant part of ammonia is produced in the kidneys. Normally ammonia is converted in the hepatocytes to the urea which is excreted with urine. The residual nitrogen is used by hepato-

cytes for the glutamate synthesis. Both damage and death of hepatocytes and portosystemic shunting of the blood impair inclusion of the ammonia in the ornithine (urea) cycle in the liver. As a result, ammonia leads to damage of astrocytes. Produced glutamate activates receptors to the N-methyl-D-aspartate (NMDA-receptors) in the neurons of the CNS with accumulation of intracellular calcium and ATP deficiency in these cells and cellular swelling. Moreover, ammonia-mediated activation of NMDA-receptors uptake of L-arginine by these neurons with subsequent activation of neuronal NO-synthase, hyperproduction of NO, oxidative and nitrozative stress and apoptotic death of neurons. Complex of NMDA-dependent pathologic effects in the CNS was determined as "excitotoxicity".

- Accumulation of gamma-aminobuthiric acid (GABA) and endogenous benzodiazepines in the gut. GABA is an inhibitory transmitter, which after passage through the blood-brain barrier interacts with postsynaptic GABAergic neurons and suppresses formation of action potentials in these cells. Endogenous benzodiazepines are able to bind with GABAergic receptors and benzodiazepines receptors of peripheral type with cortical depression.
- Formation and action of "false" neurotransmitters (octophamine and diazepam) and β-endorphins, endogenous ligands of opioidergic receptors).
- Endotoxinemia and hypercytokinemia. Proinflammatory cytokines TNF-α, IL-1 and IL-6, which concentration significantly rises in the systemic circulation, stimulate inducible NO-synthase with development of nitrozative stress and injury of neurons.
- Disorders of blood flow in the brain caused by abnormal autoregulation, which is mediated by hyperammoniemia and endotoxinemia. Such mechanism augments ischemic injury of neurons in the central nervous system.

Pathophysiological basis for treatment of hepatic encephalopathy are summarized in the Table 5-x.

Table 5-5. Management of hepatic encephalopathy: pathophysiologic grounds

Mechanisms	Treatment approaches
Hyperammoniemia	(1) Non-absorbable disaccharide lactulose, which suppresses synthesis of ammonia in the gut and stimulates its releasing from the blood in the gut; (2) Low protein diet to diminish ammonia formation; (3) Non-absorbable antibiotics (neomycin, etc.) to

	eradicate ammonia-producing bacteria; (4) Correction of obstipation to stimulate ammonia passage through the gut; (5) L-ornithine L-aspartate to stimulate urea synthesis from ammonia
"Excitotoxicity"	Protein kinase C antagonists and NMDA-receptors antagonists
Formation of "false" neurotransmitters	Diet with high contents of branched amino acids (isoleucine, leucine, valine) and with reduced amounts of aromatic amino acids (phenylalanine, tryptophan, tyrosine) to reduce synthesis of "false" neurotransmitters
Formation and action of endogenous benzodiazepines	Proteins binding with benzodiazepines and GABAergic receptors antagonists
Portosystemic blood shunting	Construction of transjugular intrahepatic portosystemic shunt, liver transplantation
Hepatocellular failure due to massive liver necrosis	Liver transplantation

11. Portal hypertension and its complications (See further).

12. Palmar erythema and "spider" hemangioma are resulted from blood vessels dilation due to local hyperproduction of vasodilators and increase in vascular permeability.

Portal hypertension

Normally portal vein carries blood from the unpaired organs of the abdominal cavity and is formed from the v. mesenterica superior and v. lienalis. It brings venous blood in the liver to detoxification. Normal blood pressure in the portal veins is approximately 5-10 mm Hg. Portal hypertension is a stable elevation of the blood pressure in the portal vein more than 12 mm Hg.

According with modification of Ohm's law, intravascular pressure (P) is in direct proportion to the blood flow (F) and resistance to the blood flow (R):

$$P=F\times R.$$

Thus, portal hypertension is a result of (1) the overfilling of the portal vein with blood or (2) rise of vascular resistance in the portal system or combination of these causes. Poiseuille law argues that even insignificant decrease in the vessel's radius leads to significant rise of vascular resistance. Such situation is common during liver cirrhosis in which alteration of tissue architecture, contraction of myofibroblasts, activation of stellate cells and contraction of vascular smooth muscle cells of hepatic veins mediated by vasoconstrictors (endothelin-1, angiotensin II, catecholamines) lead to increase of vascular resistance in the portal system. Overfilling

of the portal vein with blood may be caused by vasodilation of blood vessels in the abdominal cavity mediated by hyperproduction of vasodilators.

Portal hypertension can be classified into:

- Prehepatic;
- Intrahepatic;
- Posthepatic.

Prehepatic portal hypertension is caused by thrombosis of the portal vein, thrombosis of the v. lienalis, inborn atresia or stenosis of the portal vein, external compression of v. porta by scar or tumor, or formation of arteriovenous shunts in the abdominal cavity.

Intrahepatic portal hypertension may be due to rise of vascular resistance at the presinusoidal, sinusoidal or postsinusoidal levels. Causes of presinusoidal intrahepatic portal hypertension are following:

- Early stages of primary biliary cirrhosis and idiopatic portal hypertension;
- Nodular regenerative hyperplasia of the liver, during which regenerative nodules compress venules of the portal system;
- Myeloproliferative diseases and metastatic liver disease;
- Polycystic liver disease;
- Granulomatous liver disease (sarcoidosis, tuberculosis);
- Schistosomiasis, when helminthic eggs migrate from intestinal veins in the portal vein and stimulate granulomatous inflammation in the liver.

Intrahepatic sinusoidal and/or postsinusoidal portal hypertension is detected in:

- Liver cirrhosis;
- Acute hepatitis;
- Advanced stage of primary biliary cirrhosis and idiopatic portal hypertension;
- Venoocclusive liver diseases;
- Overdose of vitamin A. Use of vitamin A at doses 3 times upper than recommended will lead to pericellular liver fibrosis and portal hypertension.

Posthepatic portal hypertension is caused by obstruction of the v. cava inferior, right-sided heart failure, constrictive pericarditis, tricuspid regurgitation, Budd-Chiari syndrome (thrombosis of hepatic veins), fistulas between portal vein and hepatic artery, and accumulation of blood in the portal system.

Portal hypertension leads to multiply clinically significant complications:

1. Activation of portacaval shunts, which are located in the submucosal layer in the lower third of esophagus and in the upper part of the stomach (shunt between portal vein and coronary gastric vein); subcutaneous in the paraumbilical

area, and in the submucosal layer of the rectum. Esophageal varices are most dangerous, because they may rupture with development of severe esophageal bleeding due to impairment of hemostasis during liver failure. Dilation of paraumbilical subcutaneous veins manifests as “caput medusa” (head of jellyfish).

2. Splenomegaly and hypersplenism. Basic symptoms of hypersplenism include anemia, leukopenia and thrombocytopenia in the peripheral blood due to excessive degradation of blood cells by mononuclear phagocytes in the enlarged spleen and venous thrombosis in the spleen.

3. Ascites or accumulation of the extravascular fluid (transudate) in the peritoneal cavity. The most common cause of ascites is liver cirrhosis accounting approximately 80% of all cases. Pathogenesis of ascites complicated liver cirrhosis is illustrated in the Fig. 5-5.

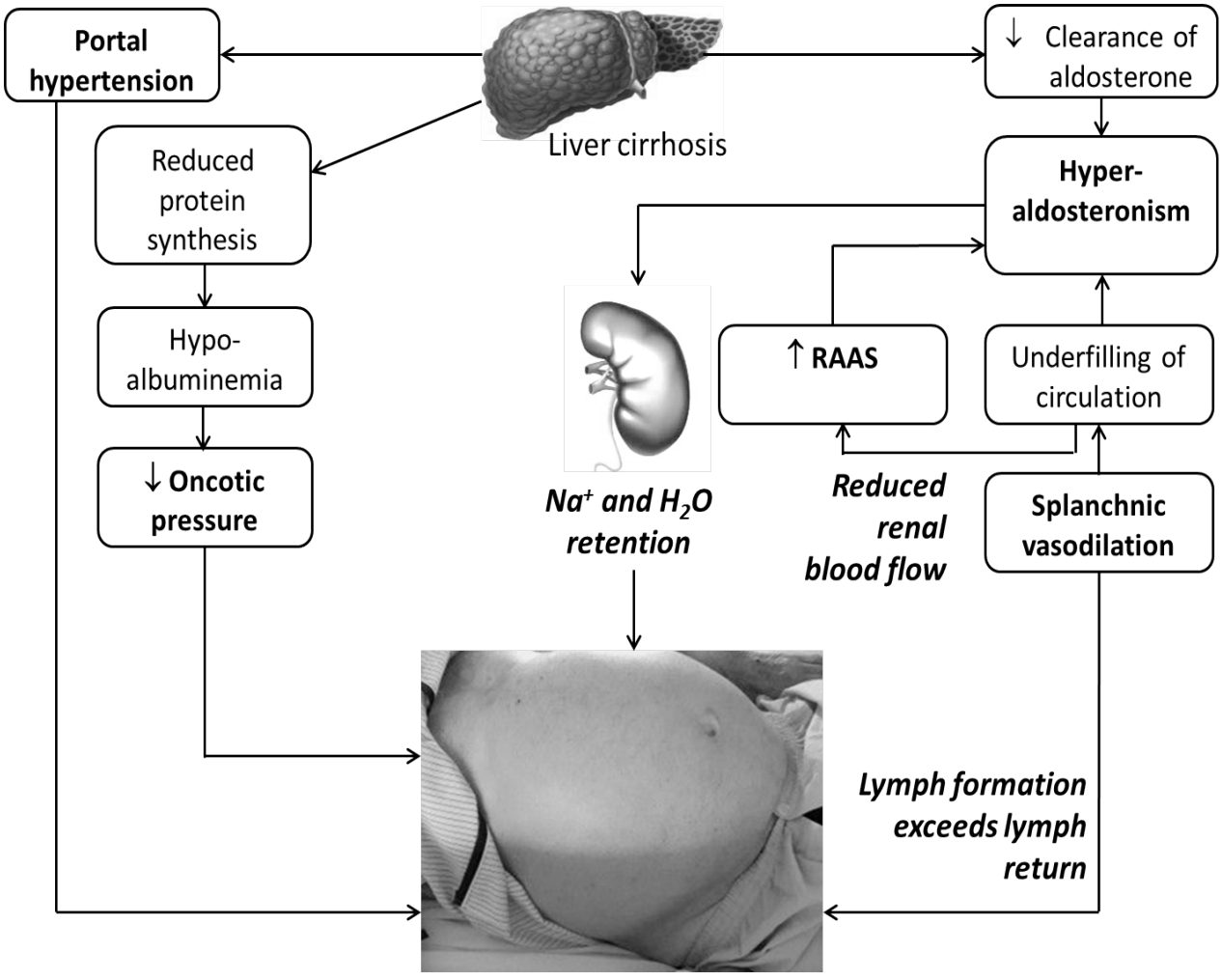


Figure 5-5. Mechanisms leading to ascites during liver cirrhosis

According with the theory of transcapillary exchange proposed by Starling, increase of blood pressure in the portal vein, which is caused by compression of portal venules by scar tissue and nodes of regeneration, leads to increase of hydrostat-

ic pressure and facilitates plasma transudation through fenestrated endothelial cells in the perisinusoidal Disse space. At physiological circumstances, transudate is absorbed in lymphatic capillaries. However, if rate of lymph production in the peritoneal cavity exceeds ability of lymphatic system and thoracic duct to absorb it, transudate begins to leak in the abdominal cavity. This process is detected during laparoscopy as "weeping liver". Activation of the RAAS is another important mechanism of ascites. Local hyperproduction of vasodilators (mainly, NO, and in less extent – glucagon) stimulates vasodilation of blood vessels in the peritoneal cavity, and as a result, hypoperfusion of kidneys with activation of juxtaglomerular cells and secretion of renin, which converts angiotensinogen to angiotensin I. Further, ACE mediates formation of angiotensin I from angiotensin II. Angiotensin II is responsible for peripheral vasoconstriction and aldosterone secretion by adrenal glands. Aldosterone stimulates kidneys to retain sodium. Hyperaldosteronism is maintained also by inability of hepatocytes to degrade it. Underfilling of the circulatory system activates SNS with secretion of ADH (vasopressin) and water retention by kidneys. Inability of hepatocytes to synthetize proteins, namely albumins in adequate amounts, results in hypoalbuminemia, which decreases oncotic pressure and facilitates transudation of plasma in the abdominal cavity.

Pathophysiological foundations for ascites management include: (1) salt restriction; (2) diuretics, starting from spironolactone-based (antagonists of aldosterone receptors); (3) albumin infusion; (4) paracentesis in severe cases; (5) intrahepatic portosystemic shunt placement.

4. Spontaneous bacterial peritonitis. Such potentially life-threatening complication is caused by different microorganisms, including *Escherichia coli, Streptococcus pneumoniae, Klebsiella* and some others Gram-negative bacteria. Pathways of their transmission in the abdominal cavity are hematogenous, lymphogenous, and through intestinal wall. Commonly spontaneous bacterial peritonitis develops in patients with relatively low content of protein in the ascitic fluid, because of opsonizing activity of the fluid is also low.

5. Hepatorenal syndrome and portosystemic encephalopathy were described earlier.

Gallstone disease

Gallstone disease is characterized by formation of stones in the gallbladder and/or in the bile ducts. If concernments are detected in the gallbladder, it is defined as cholelithiasis; presence of gallstones in the common bile duct is defined as choledocholithiasis.

Risk factors for gallstone disease are included in the "5F" rule:

F – Female;

F – Forty (incidence of the disease significantly rises after 40 years);

F – Fertile;

F – Fat (suffering from overweight or obesity);

F – Flatulence (suffering from bloating).

Predomination of females among affecting individuals is explained by estrogen-dependent cholesterol secretion in the bile and corresponding hypotonia of bile ducts which facilitates cholestasis. Sometimes initial clinical symptoms of gallstone disease manifest after pregnancy due to physiological hyperestrogenemia and physiological cholestasis. Bloating also promotes cholestasis. Hypercholesterolemia associated with obesity stimulates secretion of cholesterol in the bile with its hypersaturation with cholesterol. Other risk factors include genetic predisposition, ethnicity (Chilean females and females living in the countries of Northern Europe), overconsumption of high caloric food with rich in animal fats, and hypercholesterolemia.

Depending on gallstones structure, they may be classified into pigment, cholesterol and mixed.

Pigment gallstones may be black or brown. Main component of such gallstones is bilirubinate calcium. Black gallstones are formed usually in patients with hemolytic anemias and liver diseases, in which concentration of unconjugated bilirubin rises in the bile and it precipitates with Ca^{2+} on the surface of mucin-like glycoproteins in the bile. Brown gallstones have, as a rule, extrabladder origin and consist from calcium salts of unconjugated bilirubin, with cholesterol and calcium salts of fatty acids incorporations. These stones relate to bacterial infections of bile ducts (caused commonly by *E. coli*) or parasitic diseases (ascaridiasis, clonorchiasis) and cholestasis. Pathogenesis of brown gallstones formation is following:

1. Cholestasis $\rightarrow$ massive bacterial overgrowth $\rightarrow$ release of bacterial phospholipase A_2 $\rightarrow$ cleavage of bile phospholipids to free fatty acids;

2. Release of β-glucuronidase from *E. coli* and/or epithelial cells of bile ducts $\rightarrow$ bilirubin diglucuronide deconjugation $\rightarrow$ formation of calcium salts of bilirubin in presence of free fatty acids;

3. Decrease concentration of bile salts and phospholipids in the bile $\rightarrow$ oversaturation of bile with cholesterol $\rightarrow$ bile hyperviscosity (“sludge”, putty-like bile) $\rightarrow$ precipitation of cholesterol, calcium bilirubinate and bile acids on the mucin-like molecules and sloughed epithelial cells of bile ducts $\rightarrow$ formation of brown gallstones.

Cholesterol gallstones are most common form of concrements. At normal circumstances, cholesterol is secreted by hepatocytes in the bile, where it exists in mixed lipid micelles under optimal bile acids and lecithin ratio. Increase in cholesterol concentration and/or decrease in concentration of bile acids and phospholipids in the bile results in cholesterol crystallization and precipitation with formation of cholesterol gallstones. Activity of 7-hydroxylase, which converts cholesterol in bile acids, falls. Such “vicious circle” supports gallstones formation. An important condition for cholesterol gallstones formation is a presence of mucin-like glyco-

proteins and cytoskeletal proteins in the bile, which making “core” for future concrements.

Mixed gallstones are generated as a result of precipitation of cholesterol crystals and corresponding abnormalities of bilirubin metabolism.

Some patients with gallstones may be asymptomatic, but commonly gallstone disease may lead to multiply complications:

- Obstructive (underhepatic) jaundice
- Inflammation of bile ducts (cholangitis);
- Obstruction of gallbladder → edema of gallbladder → acute cholecystitis → gangrene or abscess of gallbladder → formation of fistula → peritonitis;
- Chronic calculous cholecystitis;
- Acute pancreatitis;
- Mucocele (hydrops of the gallbladder);
- Gallbladder cancer.

PART VI. PATHOPHYSIOLOGY OF THE KIDNEYS

Basic considerations of kidneys' functional anatomy are cornerstones for further understanding of etiology and pathogenesis of multiply renal diseases.

The kidneys are paired encapsulated organs located in the retroperitoneal area. There are no pain receptors in the kidney's tissue, so pain is detected only in those diseases which affect renal capsule or ureter. Kidneys receive approximately 25% of the total cardiac output and generate approximately 120 ml/min of glomerular filtrate. That is why almost all diseases affecting normal blood flow (for example, shock, or atherosclerotic lesion of renal artery) and normal blood composition (for instance, diabetes mellitus, autoimmune diseases) may affect kidneys.

Histologically, kidneys consist from cortex and medulla. Normally medulla has a lower blood flow than cortex, but higher metabolic activity, which makes the medulla especially susceptible to ischemic injury. The structural component of kidney is a nephron consisting from the glomerulus and renal tubule. Glomerulus is composed from afferent and efferent arterioles and tuft of capillaries which are surrounded by Bowman's capsule. Between capillary loops mesangial cells and mesangial matrix are arrangement. Glomerulus is a primary site for blood filtration, whereas renal tubules are sites of reabsorption and secretion. Renal tubule has several regions: proximal convoluted tubule, loop of Henle, distal convoluted tubule and collecting duct.

Kidneys perform different vital functions to hemostasis: excretion of waste products of metabolism; regulation of water, electrolyte and acid-base balance; controlling of mineral metabolism; metabolism of some substances; regulation of blood pressure; regulation of erythropoiesis. Kidneys are thought to play endocrine function by production of renin, metabolism of vitamin D, metabolism of vasoregulatory substances and secretion of erythropoietin. Hence, patients with renal diseases will initially demonstrate abnormalities of urine volume and/or urine composition with addition of systemic manifestations later.

Urinalysis: interpretation of abnormalities

Diurnal diuresis of healthy individuals living in temperate climate varies from 800 ml to 2500 ml. Changes of diurnal diuresis are summarized in the Table 6-1.

Table 6-1. Causes and mechanisms of polyuria, oliguria and anuria

Type of abnormal diurnal diuresis	Definition	Causes and mechanisms of development
Polyuria	Increase in diurnal diuresis above	A. Polyuria with decreased osmolality (<250 mosm/L) of the urine: increase of water consump-

	2500 ml	tion, decrease of ADH secretion and/or action. Polyuria is a result of poor water reabsorption in the renal tubules. B. Polyuria with increased osmolality (>300 mosm/L): diabetes mellitus, infusion of osmotic diuretics (mannitol), meat meal overfeeding with rise of urea concentration in the blood; damage or dysfunction of tubular epithelial cells. This type of polyuria is due to inadequate reabsorption of water and sodium.
Oliguria	Decrease of diurnal diuresis less than 500 ml	A. Fall of glomerular filtration rate in acute renal failure. B. Rise of reabsorption of water in the renal tubules as a result of ADH hyperproduction.
Anuria	Fall of diurnal diuresis below 100 ml	A. Substantial fall of glomerular filtration rate during acute renal failure or during terminal end-stage renal disease. B. Impaired urine outflow through obstructed urinary tract (urolithiasis, prostate adenoma).

The normal color of urine is yellow-straw. Rhabdomyolysis with releasing of myoglobin from damaged skeletal muscles may give brown coloration tom the urine. Accumulation of conjugated bilirubin in the urine also leads to its brown coloration. Some drugs and dyes may add specific coloration to the urine.

Urinary pH is usually approximately 5 (acidic) due to daily acid excretion, but may vary from 4.5 to 8.5. Stable acidic pH of urine predisposes to renal stones formation, especially composed from uric acid salts (urates). Elevation of pH to alkaline value is seen after meal stimulating HCl excretion, in vegetarians or specific infections (for instance, Proteus, which splits urea), and also in metabolic acidosis with normal or decreased anion gap. Stable alkaline pH value is detected in renal tubular acidosis. Alkali urinary pH facilitates formation of renal stones from oxalates and phosphates.

Urine specific gravity reflects concentration of high molecular weight solutes (glucose, proteins, contrast dye, etc.). Normally urine specific gravity fluctuates during a day from 1002 to 1030. Usually morning probe of urine is most concentrated. If urine morning specific gravity exceeds 1018, kidneys' ability to concentrate urine is thought to be normal. Glycosuria increases urine specific gravity, whereas inability of kidneys to concentrate urine results in decrease of urine specific gravity. Severe dehydration results in increase of urine specific gravity. Decrease in urine specific gravity is detected after overconsumption of fluids, low salt and/or low protein diet, diuretics overdose, deficiency of ADH, and renal tubular dysfunction. Stable excretion of urine with decreased gravity or fixed specific gravity (isostenuria) indicates chronic kidney disease (CKD) complicated with dif-

ferent renal and extrarenal pathologies.

Chemical testing of a urine probe may detect glucose or protein. Glycosuria (presence of glucose in the urine) is seen in patients with diabetes mellitus, when glucose threshold overcomes. As a rule, glycosuria is detected if concentration of glucose in the blood is more than 8.88 – 9.99 mmol/l. However, damage of proximal convoluted tubules playing a central role in the glucose reabsorption, may also lead to glycosuria.

No any ketone bodies are detected in the urine normally. Detection of ketones (ketonuria) is a hallmark of insulin deficiency in diabetic patients and/or food starvation, when lipolysis tries to compensate lack of energy.

Different low- and high molecular proteins are excreted in urine in small amounts (30-50 mg/day) in physiological conditions, and these very low concentrations can't be detected during routine urinalysis. At normal circumstances, most part of filtered protein in the glomeruli is reabsorbed in the proximal tubules, however, some proteins (for instance, Tamm-Horsfall protein, See later) is secreted in the urine. **Proteinuria** is a release of proteins in the urine at amounts more than 50 mg/day. It can be classified into "functional" and pathological; selective and non-selective. According with basic mechanism of development, proteinuria may have glomerular origin; tubular origin or it may be caused by protein overload. To better understand causes of proteinuria of glomerular origin it is important to recognize cellular and molecular structure of the "glomerular filter" (Fig. 6-1):

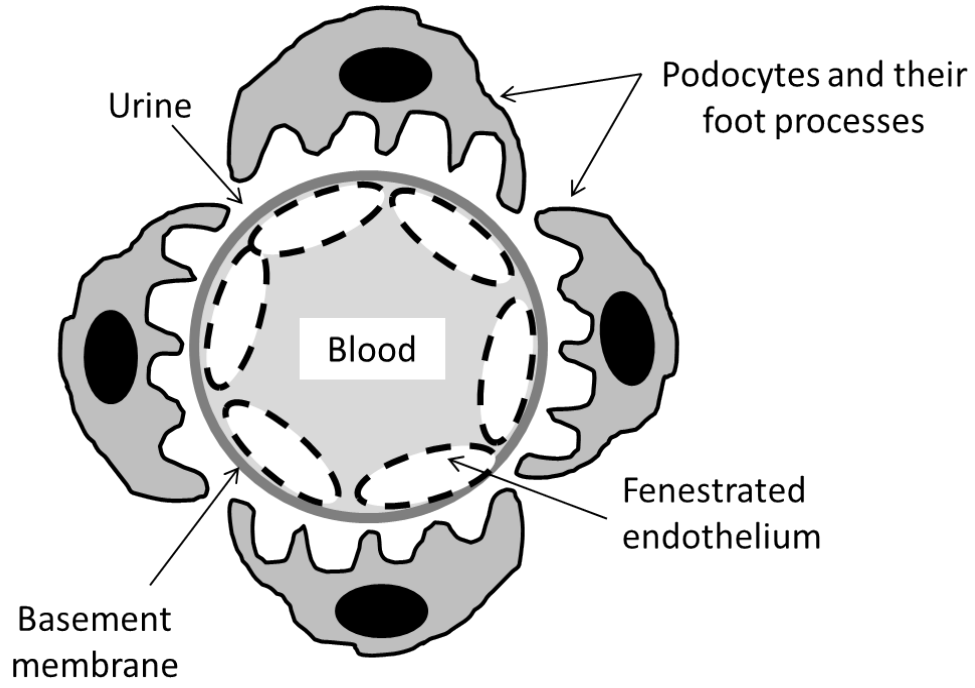


Figure 6-1. Schematic structure of a normal "glomerular filter"

It is important to clarify, that at physiological circumstances leakage of proteins in the urinary space is prevented by normal anatomical barrier (See Fig. 6-1),

negative electrostatic charge of renal capillary wall and podocytes foot and normal renal hemodynamic. A normal "glomerular filter" consists from three layers: fenestrated endothelial cells with polyanionic glycocalix above allowing passing molecules, but not blood cells; basement membrane consisting from type IV collagen, laminin, anionic proteoglycans, fibronectin and some glycoproteins, and podocytes having multiply foots and processes, which form a slit diaphragm. Small proteins (lysozyme, β_2-microglobulin, ribonuclease, light chains of immunoglobulins, retinol-binding protein) pass freely through the glomerular filter, but are almost entirely reabsorbed by epithelial cells of convoluted tubules. Albumins due to their small size (diameter is approximately 3.6 nm) are smaller than pores, but they are blocked by negative charge of fenestrated endothelial cells and that is why albumins normally absent in the urine. Due to its polyanionic structure basement membrane and podocytes foot processes also are negatively charged thus pushing away negatively charged macromolecules including albumins. Loss of the negative charge leads to excretions of albumins, and further, larger proteins with urine.

Proteinuria can be classified into selective and non-selective. Selective proteinuria is characterized by a presence of proteins with molecular weight less than 65,000 kDa (mainly albumins). Non-selective proteinuria prognostically is less favorable than selective proteinuria, because it occurs after more pronounced damage of "glomerular filter" allowing passing proteins with middle and high molecular weight in the urinary space. In such situations, α_2-macroglobulins, β-lipoproteins, γ-globulins are predominant urine proteins.

Microalbuminuria is a specific kind of selective proteinuria. Normal excretion of albumins with urine per day don't exceed 30 mg. Microalbuminuria is excretion of small but abnormal amounts of albumins with urine, usually 30-300 mg/day, or an albumin/creatinine ratio of 2.5-25 mg/mmol in males and 3.5-25 mg/mmol in female. Microalbuminuria is a marker of early kidney diseases (in patients with diabetes mellitus, arterial hypertension, metabolic syndrome, and other pathologies) and predictor of coronary heart disease and mortality (Fig. 6-2). Release of albumins in the urine space through a "glomerular filter" stimulates local inflammatory response with recruitment of inflammatory cells, transition of tubular epithelial cells to myofibroblasts, secretion of growth factors, and synthesis of collagen and other components of extracellular matrix with development of glomerulosclerosis and compensatory hyperfiltration in residual nephrons. Excessive hemodynamic load damages other nephrons with releasing DAMPs and perpetuation of inflammatory response and more severe damage of "glomerular filter" leading to overt proteinuria. In fact, "vicious circle" is formed. Moreover, figuratively speaking, microalbuminuria is a "mirror", which reflects generalized endothelial dysfunction including endothelial dysfunction of coronary arteries. As a result, individuals with documented microalbuminuria demonstrate high rate of atherogenesis, high risk of thrombosis and increased general mortality. Backgrounds to microalbuminuria management are summarized in the caption to the Fig. 6-2.

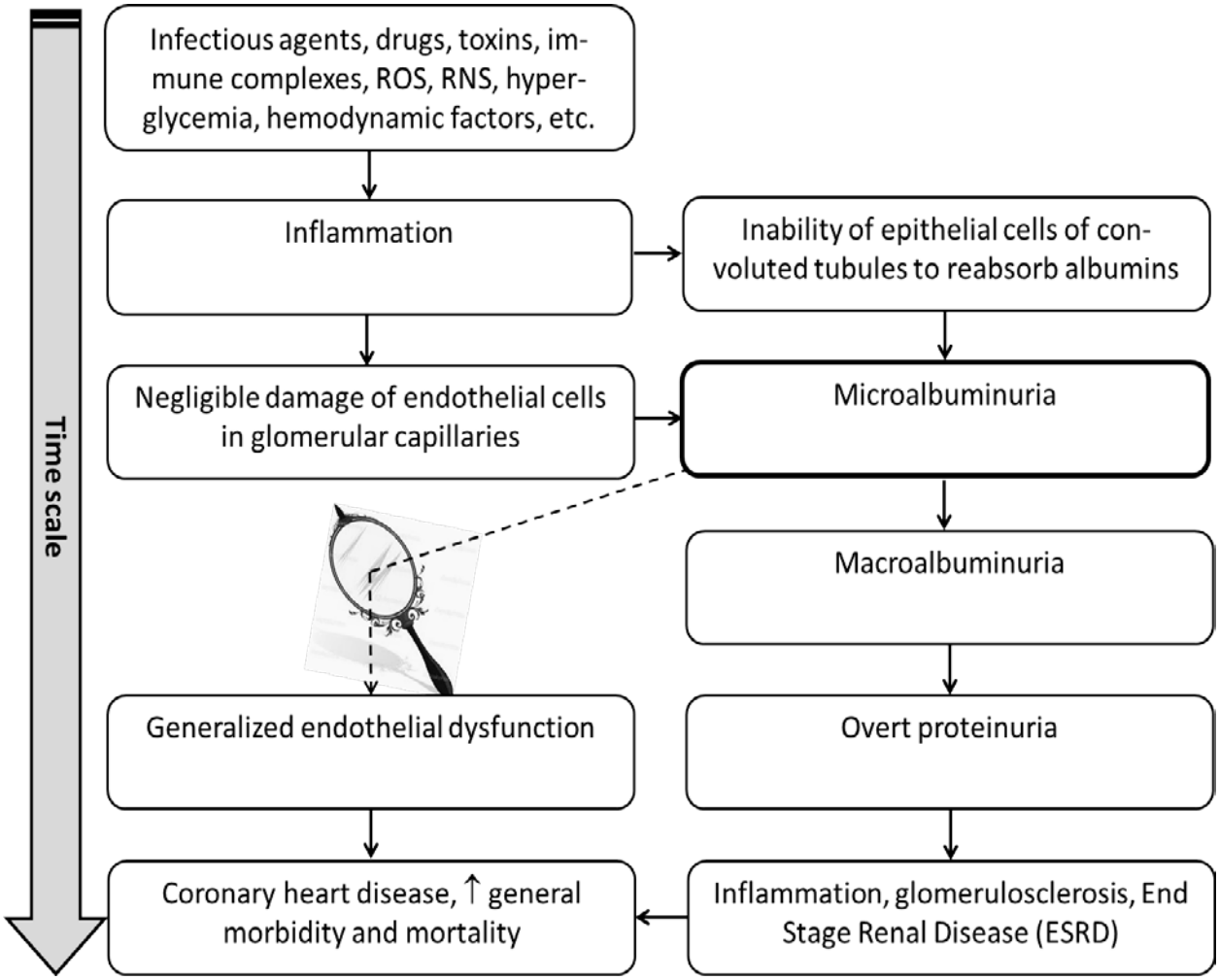


Figure 6-2. Pathophysiological significance of microalbuminuria

Lifestyle correction (cessation of smoking, body weight reduction, adequate level of physical activity, correct diet with protein restriction), management of underlying diseases (diabetes mellitus, arterial hypertension, metabolic syndrome, etc.), RAAS inhibition (with ACE inhibitors, antagonists of AT1R, direct renin inhibitors, endothelin A receptor antagonists and statins were shown to be effective as a drugs delaying progression of microalbuminuria to overt proteinuria

Local inflammation in renal glomeruli results in proteinuria caused by damage of renal filter. Increased capillary wall permeability, renal hyperperfusion and alterations of oncotic pressure may facilitate proteinuria of glomerular origin. This type of proteinuria is common in glomerulonephritis, amyloidosis of kidneys, diabetic nephropathy, glomerulosclerosis complicated arterial hypertension, renal artery thrombosis and congestive heart failure.

Proteinuria of tubular origin is resulted from decreased reabsorption of filtered low molecular weight proteins in proximal tubular cells. Particular features of this type of proteinuria include (1) predomination of β_2-microglobulin over albumins in excreted urine and (2) absence of high molecular weight proteins in the

urine. Proteinuria of tubular origin appears after damage of tubular epithelial cells and interstitium in interstitial nephritis, pyelonephritis, acute tubular necrosis, graft rejection, and inborn tubulopathies.

Proteinuria caused by protein overload is detected in patients having increased synthesis of low molecular weight proteins (light chains of immunoglobulins, hemoglobin, myoglobin), when these proteins pass freely through "glomerular filter", but ability to reabsorb them is decreased. Such situation is common in patients with multiply myeloma, myoglobinuria, and lysozymuria in leukemic patients. Plasma or albumin infusion in great amounts also may lead to such type of proteinuria.

Pathogenesis of "functional" proteinuria is yet poorly understood; it may be classified into orthostatic (after prolonged standing or walking), idiopathic, related to extreme physical exertion, or associated with fever. This proteinuria is nonselective and has glomerular origin. Orthostatic "functional" proteinuria is detected in children and young individual and usually regresses completely following 5-10 years.

Normally only single erythrocytes (0-1) in the microscopic field are detected in the urine sample. Hematuria, or presence of blood (red blood cells, excepting menstruating females) in the urine may be gross or microscopic. Overt, gross hematuria (macrohematuria) may originate from urethra, prostate, bladder, and ureter. Urine sample is cloudy, with colour of "meat slops". Macrohematuria is a leading symptom of urolithiasis, nephrolithiasis and tumors. Occult hematuria (microhematuria) is characterized by a presence of <100 erythrocytes in the microscopic field. According with Nechiporenko's probe, normally less than 1×10^3/ml red blood cells present in the urine. Nechiporenko's probe is useful method for evaluation of microhematuria. Detection of structurally changed erythrocytes during phase-contrast microscopy indicates their glomerular origin. However, microhematuria may be detected after trauma, extreme physical exercises, bleeding disorders and vascular diseases including hypertensive vascular disease.

Urinary sediment normally contains leukocytes (0-1 in the microscopic field in males and 5-6 in the microscopic field in females or $<4\times10^3$/ml with Nechiporenko's method). Excretion of leukocytes in the urine in greater amounts is determines as leukocyturia (pyuria). Leukocyturia may have renal or urinary tract origin; it may be infectious or aseptic.

Urinary casts are cylindrical bodies which were shaped in the distal tubular lumen. According with their composition, urinary casts may be hyaline, granular and cellular. Hyaline casts consist predominantly from Tamm-Horsfall uroprotein, which is secreted by cells in ascending Henle's loop and distal tubules. These casts are most common. Granular casts are formed mainly from damaged tubular cells and their detection indicates tubular injury. Cellular casts are composed predominantly from leukocytes or erythrocytes; their presence in the urine probe points to exudative, hemorrhagic or destructive changes in nephrons.

Detection of crystals in the urine sample may have dual significance. For ex-

ample, some crystals usually haven't any pathologic significance (calcium oxalate crystals, uric acid crystals, sodium urate, and calcium phosphate); some crystals (hexagonal crystals in cystinuria or phosphate crystals in infectious diseases affecting urinary tract) are pathological.

Different bacteria may be seen in urine sediment in patients with multiply infectious diseases affecting kidneys and urinary tract.

Simplest tests of kidneys' functions assessment

The best marker of renal excretory function is the glomerular filtration rate (GFR), which is assessed by renal clearance. Renal clearance of any substance is thought to be a volume of plasma that is completely cleared of the substance by the kidneys per unit time. Different substances (polysaccharide inulin, creatinine, an inhibitor of cysteine protease cystatin C or radioactive labeled ^{51}Cr-EDTA) were proposed to study renal clearance, but creatinine is most employed in the routine clinical practice despite its poor sensitivity in early stages of kidney diseases. Creatinine is a product of creatine degradation, which is released from normal skeletal muscles. Creatinine is produced at constant rate, freely passed through "glomerular filter" and neither reabsorbed nor secreted in significant amounts by tubular epithelial cells. GFR can be calculated according with the formula:

$$GFR = U_{cr} \times V / P_{cr}, \text{ where}$$

U_{cr} is urine concentration of creatinine; V is urine flow rate (per minute or 24 hours); P_{cr} is plasma concentration of creatinine. Normally GFR varies from 115 to 125 ml/min. To standardize GFR it is calculated to a body surface area of 1.73 m^2. In individuals with chronic kidney disease (formerly it was termed as "chronic renal failure") GFR falls below 60 ml/min/1.73 m^2. End stage renal disease (ESRD) is characterized by marked fall of GFR, when it is less than 5% compared to normal value.

GFR is evaluated in parallel with blood urea nitrogen (BUN) and creatine concentration in the blood. Urea is produced by the liver (25-30 g/day) from metabolism of degrading proteins. Normal BUN varies from 2.9 to 8.9 mmol/l, normal creatinine concentration is 50-100 mmol/l. There are some basic causes of BUN elevation:

- High-protein diet with increased catabolism of proteins;
- Massive tissue breakdown with proteins degradation;
- Bleeding from gastrointestinal tract, when blood proteins are degraded in the intestine to ammonia, which is transported by portal vein in the liver with subsequent conversion to the urea;
- Dehydration with fall of GFR;
- Kidney diseases; however, it is important to know that approximately 2/3 of kidneys' function must be impaired before evaluation of significant rise of BUN.

Normal BUN-creatinine ratio is 10:1. Rise in BUN-creatinine ratio to 15:1 indi-

cates prerenal diseases, decrease the ratio less than 10:1 is informative in liver diseases, low protein diet and may be seen after dialysis.

Concept description of kidney diseases and their main syndromes

According with anatomical point of view, at the entry-level renal diseases might be classified into glomerular (glomerulonephritis and glomerulopathies); tubular (tubulopathies, acute tubular necrosis); interstitial diseases and diseases affecting blood vessels. However, primary injury of selected structure in case of disease progression will lead to damage other morphological components of kidneys with development ESRD in future. Particular features of glomerulonephritis are immune-mediated injury of glomeruli; tubular and interstitial disorders have toxic agents and infectious as causative agents. According with pathophysiological point of view, kidney diseases are subdivided into infectious, toxic, immunologic, metabolic, infiltrative and hemodynamic; inherited or acquired; prerenal, renal and postrenal. Prerenal causes are due to diminished renal blood flow, renal causes directly affect parenchyma, whereas postrenal diseases are resulted from impaired urine outflow.

Nephritic syndrome vs. nephrotic syndrome

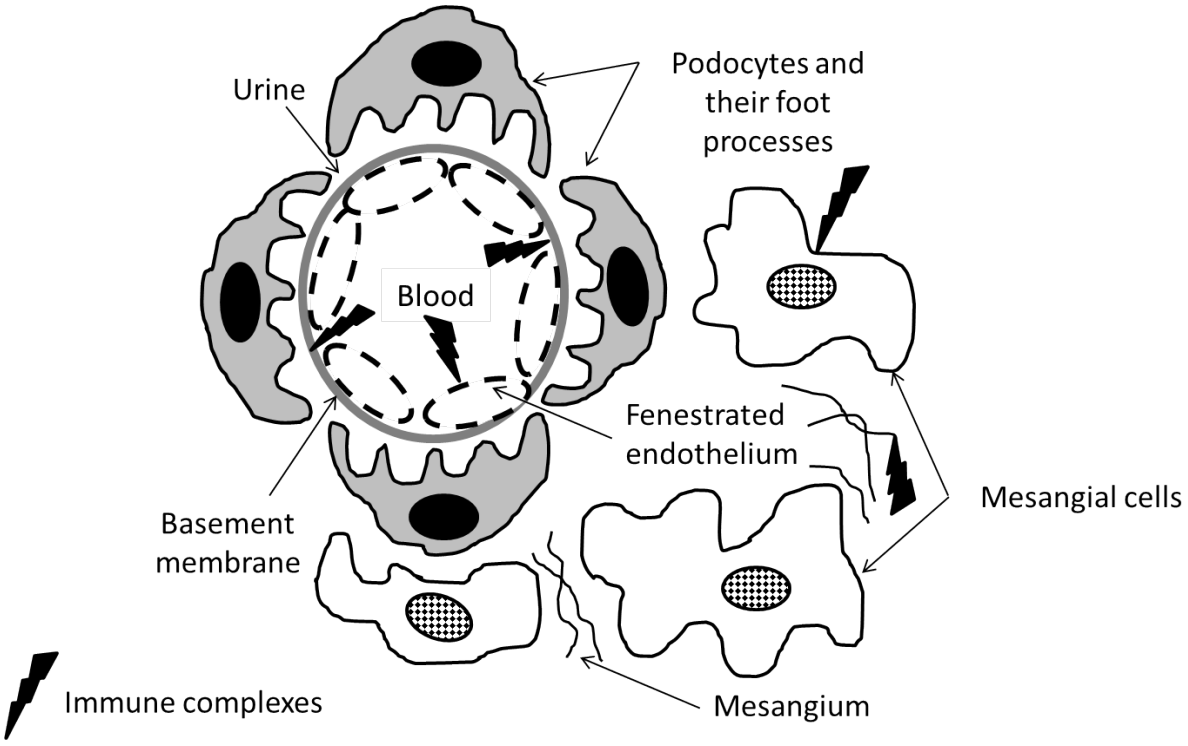
Comparative characteristic of nephritic and nephrotic syndrome is summarized in the Table 6-2.

Table 6-2. Comparison of nephritic and nephrotic syndrome

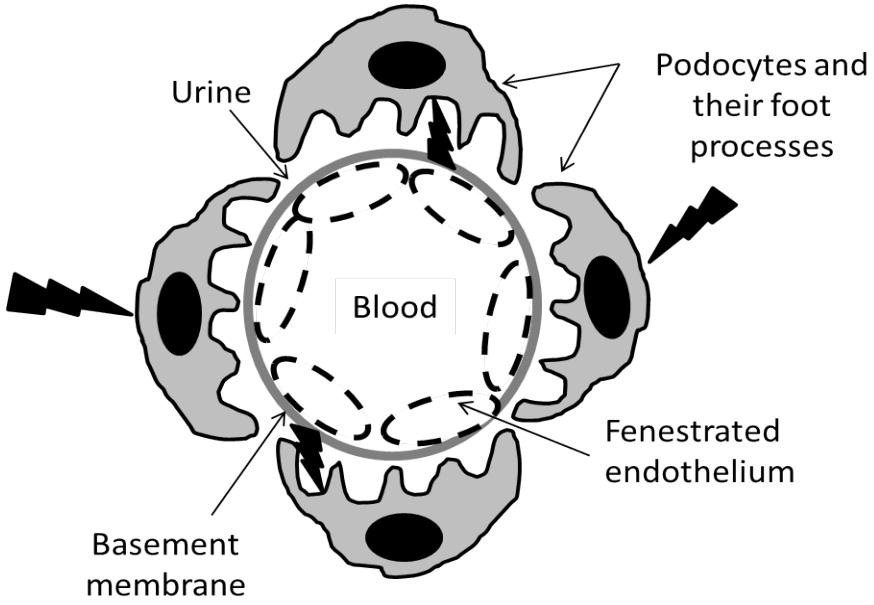
Features	Nephritic syndrome	Nephrotic syndrome
Site of predominant immune complexes deposition in the glomeruli	Surface of fenestrated endothelial cells, basement membrane, mesangium	Surface of podocytes (both at and under)
Severity of cellular immune response	Severe (due to close proximity to blood-derived leukocytes and inflammatory mediators)	Weak
Rate of inflammation resolution	High in case of well-controlled inflammation	Slow
Degree of injury	Profound in case of uncontrolled severe inflammation	Limited
Urinalysis	Oliguria, variable degree of proteinuria, occult or gross hematuria, leukocyturia	Profound proteinuria lasting from several months to several years until correct management
Additional findings	Secondary arterial hypertension due to RAAS activation, elevated BUN and creatinine,	Hypoproteinemia, hypoalbuminemia, hypooncotic edema, hyperlipidemia,

	edema	thrombophilia, arterial hypertension

Due to high rate of renal blood flow and their specific function, glomeruli are susceptible to deposition of immune complexes (Fig. 6-3).



A. Deposition of immune complexes during nephritic syndrome



B. Deposition of immune complexes during nephrotic syndrome

Figure 6-3. Sites of immune complexes deposition

Nephrotic syndrome, which is characterized by (1) severe proteinuria (>3.5

g/24 h), (2) hypoproteinemia, hypoalbuminemia, (3) severe edema and (4) hyperlipidemia is most commonly caused by membranous nephropathy, glomerulopathies associated with systemic diseases, epithelial cell (minimal change) disease, focal segmental glomerulosclerosis, and less commonly – membranoproliferative glomerulopathies and other primary glomerulopathies. Simplified pathogenesis of nephrotic syndrome is illustrated in the Fig. 6-4.

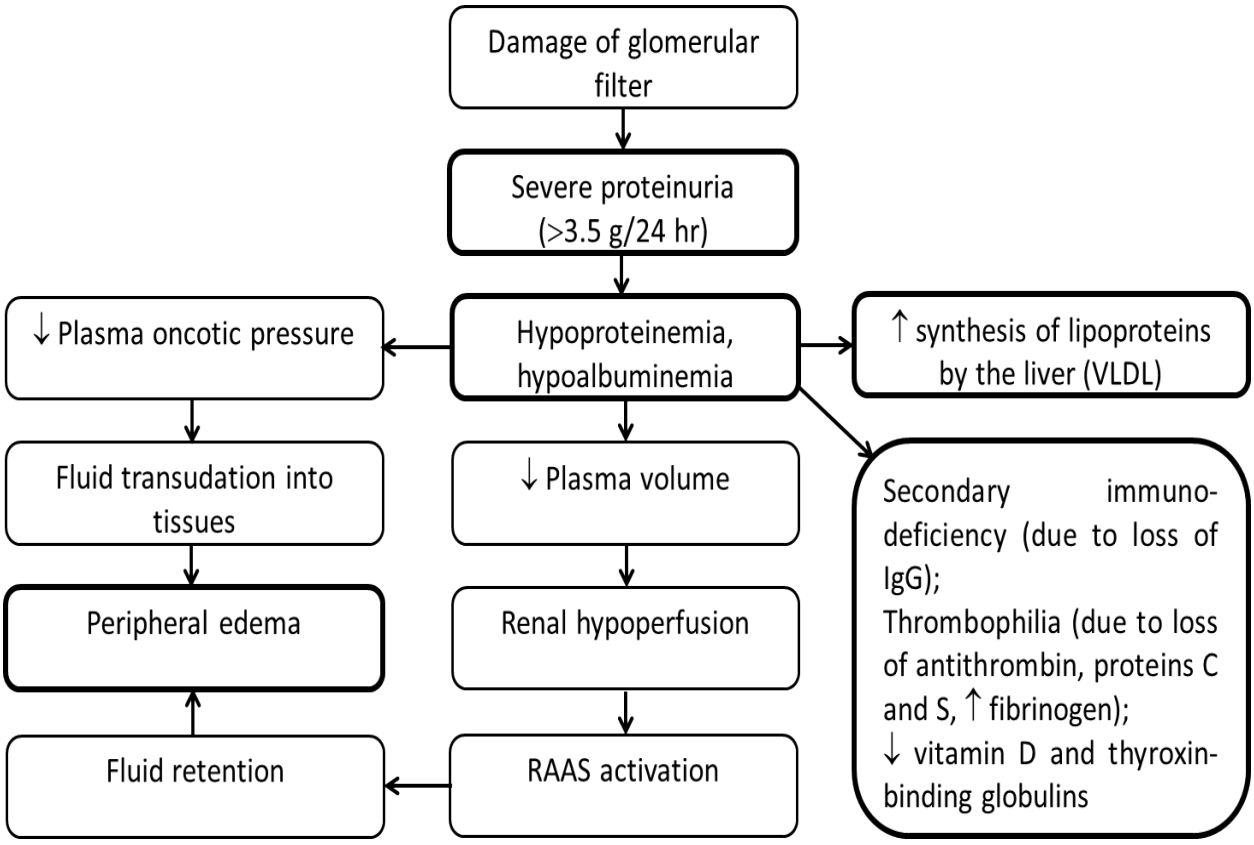


Figure 6-4. Pathophysiology of nephrotic syndrome

RAAS, Renin-Angiotensin-Aldosterone System; VLDL, Very Low Density Lipoproteins

Pathophysiological characteristic of selected glomerular diseases

Disease affecting glomeruli with evident inflammation is called glomerulonephritis, which may be inherited or acquired, primary or secondary. The latter is associated with underlying diseases, for instance, autoimmune diseases such as systemic lupus erythematosus, Goodpasture syndrome; diabetes mellitus, amyloidosis, vasculitis, etc. Primary glomerular diseases include minimal change disease, focal and segmental glomerulosclerosis, membranous nephropathy, acute postinfectious glomerulonephritis, membranoproliferative glomerulonephritis, Ig A nephropathy and chronic glomerulonephritis. Inherited diseases affecting glomeruli are resulted from gene mutations affecting proteins of the slit diaphragm (nephrin or podocin) or collagen (Alport's syndrome). Fabry's disease (lysosomal storage disease) is also example of hereditary glomerulopathy.

Glomerular diseases with predominantly nephritic syndrome

In most forms of glomerulonephritis inflammation is driven by humoral and cellular mechanisms. Glomeruli are sites of immune complexes formation and deposition. During poststreptococcal glomerulonephritis or glomerulonephritis associated with systemic lupus erythematosus immune complexes are carried with blood and deposited in the mesangium, under fenestrated endothelium or between basement membrane and podocytes (See Fig. 6-3A).

Poststreptococcal glomerulonephritis typically affects children suffering from infections caused by strains of type M β-hemolytic Streptococci. Glomerulonephritis starts 7-10 days after infection. Cross-reaction between bacterial antigens and components of glomerular basement membrane leads to immune complexes formation. Immune complexes activate complement system with production of anaphylotoxins, opsonins and C_5-C_9 attack complex with recruiting and activation of leukocytes, stimulating phagocytosis and damage of "glomerular filter" by ROS, RNS and proteases. In fact, outcome of glomerulonephritis is strongly dependent on the causative agent, properties of immune complexes and their amounts, ability of neutrophils and macrophages to phagocytose them, locally produced proinflammatory and proresolving molecules, genetic predisposition and many other factors. Poststreptococcal glomerulonephritis is a disease with potentially favorable prognosis.

However, persistent glomerular injury, for instance, during autoimmune diseases, leads to hyperfiltration in unchanged nephrons and more severe protein leak through damaged glomerular filter in the interstitium. Locally produced angiotensin II promotes inflammation and recruits interstitial mononuclear cells. During persistent inflammation neutrophils are replaced by macrophages and T-lymphocytes. Proinflammatory cytokines, chemokines, growth factors TGF-β, FGF, PDGF mediate epithelial-mesenchymal transition, or transformation of some tubular epithelial cells detached from the basement membrane, to interstitial fibroblasts having synthetic phenotype. These cells produce collagen, fibronectin and other components of extracellular matrix with development of glomerulosclerosis. Atrophy of tubular epithelial cells develops in parallel. Hyperfiltration in residual nephrons create "vicious circle" with stepwise loss of nephrons and development of ESRD.

Ig A nephropathy (Berger's disease) is a most common cause of nephritic syndrome in children and adults. It is resulted from deposition of antigen-IgA complexes of IgA in the mesangium with subsequent activation of complement system via alternative pathway and inflammation with a damage of "glomerular filter" and recurrent hematuria.

Glomerular diseases with predominantly nephrotic syndrome

Minimal change disease ("nil lesion", lipoid nephrosis) is a most common cause of nephrotic syndrome in children. It is developed usually as a primary dis-

ease, but sometimes associated with Hodgkin's lymphoma, allergic diseases or use of NSAIDs. Biopsy of kidney shows no any changes in glomeruli during light microscopy, but electron microscopy reveals damage of podocytes and their foot processes. Activation of T-cells and releasing from these cells proinflammatory cytokines was shown to be most important pathogenetic mechanisms of impairment function of the slit diaphragm. Tubular cells reabsorb passed through the damaged filter droplets of lipoproteins. This fact explains old term "lipoid nephrosis" applicable to this disease formerly.

Focal segmental glomerulosclerosis histologically is characterized by segmental sclerosis affecting only a small minority of glomeruli. It affects adults more common than children. Basic mechanism of injury is damage of mainly podocytes manifesting as non-selective proteinuria in connection with hematuria, hypertension and renal failure. It may be primary or secondary, which is associated with viral infections, arterial hypertension, some drugs (heroin and analgesics), lymphoma, sickle cell disease and some hereditary pathology affecting kidneys. Scarring, in fact, is due to poor controlled resolution response during inflammation and activation of fibroblasts.

Membranous glomerulonephritis (membranous nephropathy) affects males of 30-50 years most frequently than females. Usually it is primary disorder, but may be secondary associating with different malignancies, infections or rheumatic diseases and some drugs (gold salts, captopril, NSAIDs, penicillamine). Main histological hallmark of the membranous glomerulonephritis is a thickening of basement membrane of glomeruli due to deposition of immune complexes in the basement membrane and under podocytes, activation of complement to C_5-C_9 and related injury. The diseases manifests by severe non-selective proteinuria.

Membranoproliferative glomerulonephritis (mesangiocapillary glomerulonephritis) histologically is displayed by thickening of basement membrane and proliferation of mesangial cells and endothelial cells. It is developed or primarily or secondary, in links with underlying diseases like as bacterial endocarditis, systemic lupus erythematosus, hepatitis C, cryoglobulinemia, malignancies or complement receptor deficiency. Immune complexes are formed in the blood or formed locally in the kidneys. They deposit in the mesangium or under endothelial cells and activate complement with C_3 formation. In some individuals, antibodies against C_3 are detected, which are called C_3 nephritic factor. Factor H (mutated protein regulating complement activity) also presents in some patients. Complement-mediated inflammation and activation of humoral and cellular-mediated inflammatory response produce damage of "glomerular filter" with epithelial-mesenchymal transition and stimulation of cellular proliferation. Initially this disease may manifest as nephritic syndrome transforming to nephrotic syndrome. Membranoproliferative glomerulonephritis usually has poor prognosis, with development of ESRD.

Generally, renal function during glomerulonephritis depends on the severity and resolution of inflammation. Whereas resolution of inflammation results in a

potentially recoverable impairment of function, persistent glomerular injury produces progressive loss of normal renal function by following mechanisms (Fig. 6-5).

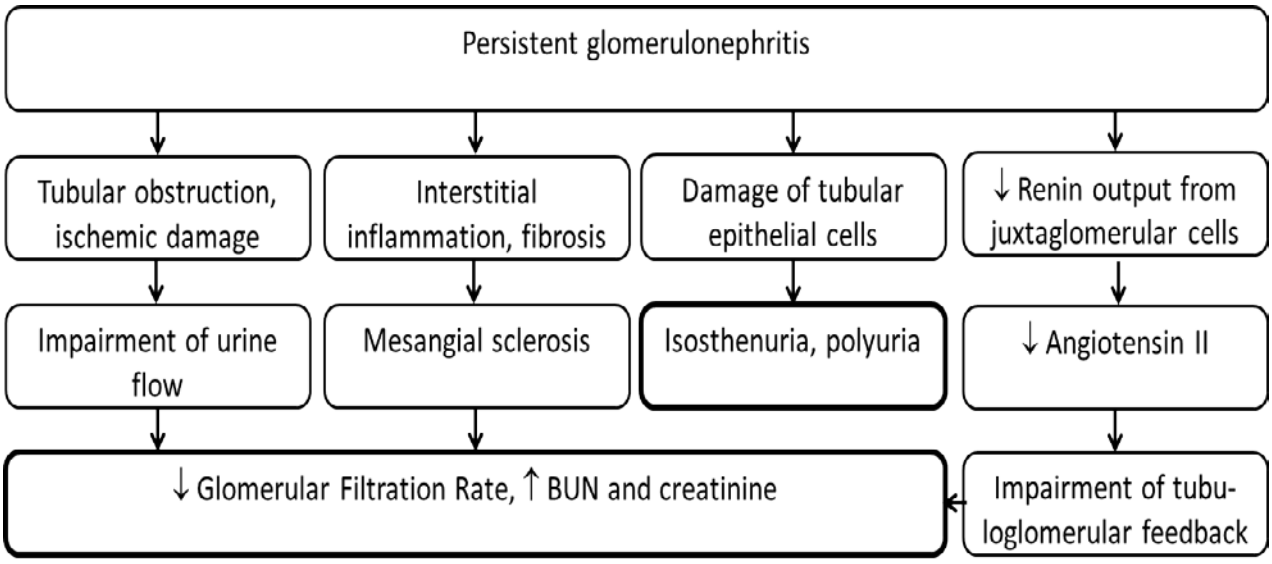


Figure 6-5. Mechanisms of glomerular diseases progression

It is important to note, that coexisting diseases and abnormalities such as arterial hypertension, diabetes mellitus, obesity, smoking, overconsumption of protein, hyperlipidemia, inborn reduction of nephron number in premature neonates, especially having body weight at birth lower than 2.5 kg, may accelerate glomerular diseases progression.

Pathophysiological basis for treatment of glomerulonephritis: (1) in case of secondary glomerulonephritis it is necessary to correct underlying diseases carefully; (2) antibiotics in poststreptococcal glomerulonephritis; (3) suppression of inflammation with glucocorticoids and/or immunosuppressive drugs (alkylating agent cyclophosphamide, azathioprine, mycophenolate mofetil) or alternatively cyclosporine, tacrolimus, rituximab or anti-CD20 antibodies; (4) diuretics (furosemid) alone or in combination with albumin to relieve edema in nephrotic syndrome; (5) correction of hyperlipidemia in patients with nephrotic syndrome; (6) treatment of secondary arterial hypertension with ACE inhibitors or angiotensin receptor blockers.

Tubulointerstitial disorders

Different pathogens affect both renal tubules and interstitium that is why such disorders are discussed in parallel as “tubulointerstitial disorders”. Generally, these disorders relate to inflammatory process affecting tubules and interstitium (interstitial nephritis) and acute tubular necrosis (See later). Depending on etiology, inflammatory process may be determined as pyelonephritis or interstitial nephritis. Pyelonephritis is an inflammation of renal pelvis with involvement in the pathological process others renal structures induced by bacterial infection. Intersti-

tial nephritis is caused by drugs, toxins, metabolites, physical phlogogens, and immune-mediated mechanisms. Tubulointerstitial disorders can be classified as following:

- Acute vs. chronic tubulointerstitial disorders. Acute disorders may manifest as acute kidney failure, whereas chronic disorders often progress to end stage renal disease.
- Primary vs. secondary tubulointerstitial disorders. Primary disorders affect the tubules and interstitium without significant involvement of the glomeruli; however, they sometimes are involved in the pathological process at late stage of disease. Secondary tubulointerstitial disorders initially affect glomeruli or vasculature, with addition of tubules and interstitium damage with time.

  Loss of kidneys function in tubulointerstitial disorders depends on the site of primary lesion (Fig. 6-6).

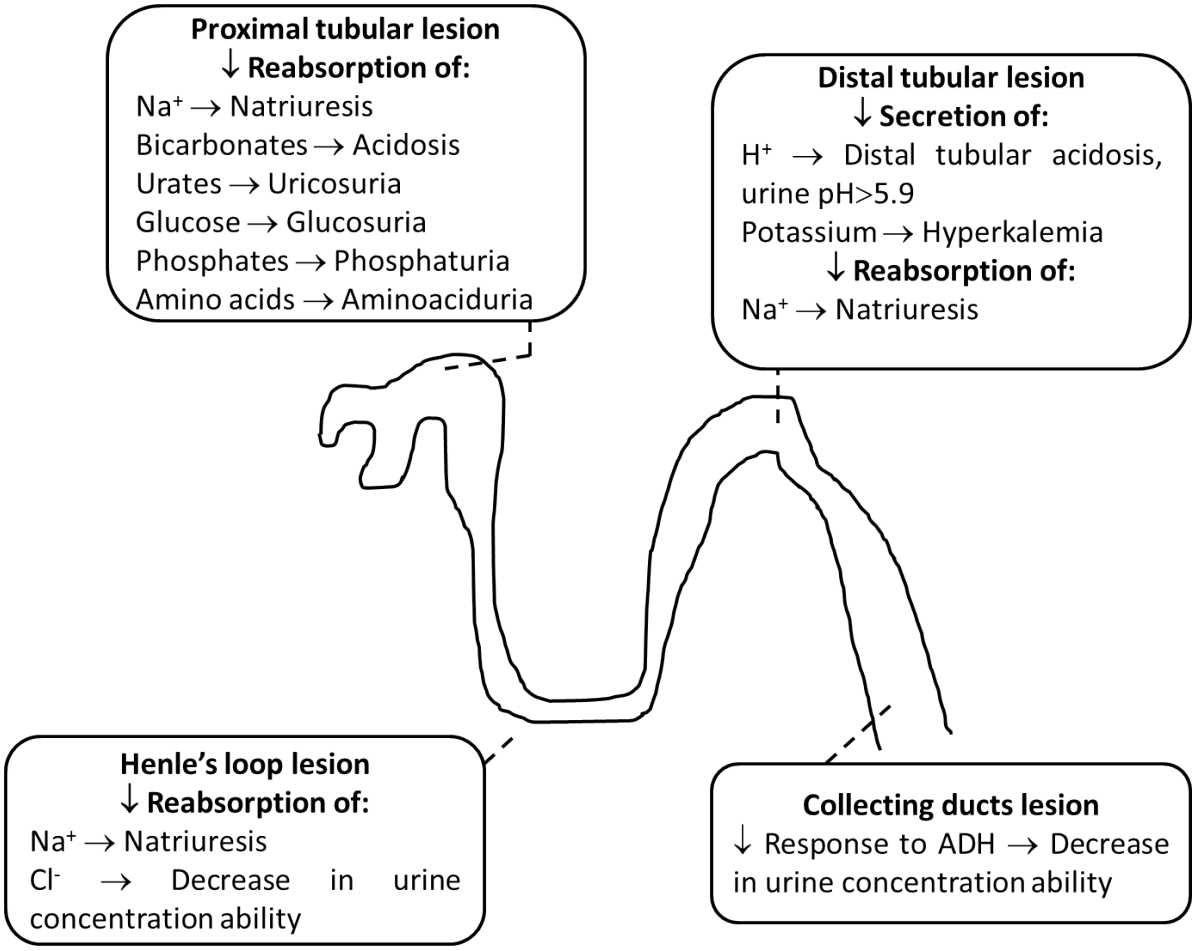


Figure 6-6. Patterns of tubular dysfunction in tubulointerstitial diseases

Pyelonephritis is an infectious disease affecting renal pelvis. Infections (E. coli, Proteus, Pseudomonas, Klebsiella, Enterobacter, Staphylococcus, etc.) reach the kidneys from lower urinary tract as ascending infection usually or by hematogenous spreading during infectious endocarditis or septicemia. Lower urinary tract

infections and ascending pyelonephritis most commonly is registered in females than in males due to close proximity of female urethra to the anus and anatomical feature of the female urethra, which is shorter and wider than male urethra. Use of instruments in the urinary tract facilitates pyelonephritis. Pregnant females often develop infections of the lower urinary tract and renal pelvis due to abnormal renal outflow, reflux of urine from the bladder in the ureters and specific changes of innate and adaptive immunity during pregnancy, which are mediated by hormonal changes.

In fact, pyelonephritis is an example of an infectious process, whose outcomes depend on properties of microorganisms and host. That is why obstruction of urinary tract at any level, vesicoureteral reflux (reflux of bladder urine in the ureter) diabetes mellitus, immunosuppressive agents, other causes of secondary immunodeficiency facilitate bacterial growth, colonization of renal pelvis and persistence of microorganisms on the surface of epithelial cells and in the urine.

Inflammation in renal pelvis leads to leukocyturia (pyuria) and bacteriuria. Clinically pyelonephritis is manifested by fever, weakness, pain at the costovertebral area, dysuria and urinary urgency.

Pathophysiological basis for treatment: antibacterial therapy according with sensitivity of microbiota to antibacterial drug.

Interstitial nephritis is caused by drugs, toxins, metabolic abnormalities and some rare diseases. Most commonly drug-induced interstitial nephritis is caused by synthetic antibiotics, especially penicillins, thiazide diuretics, NSAIDs, and phenacetin-containing analgetics. Basically, these reactions are examples of the Type IV or Type I hypersensitivity reactions, in particular, mediated by Th2 with hyperproduction of IgE (See Table 13-1 in the Textbook “General pathophysiology: the essentials”). Drugs play role of haptens, which bind with plasma proteins or extracellular parts of tubular proteins. APCs or damaged tubular epithelial cells expressing MHCII molecules recognize modified proteins and present them to T-cells which interact with B-cells and stimulate them to produce immunoglobulins. Releasing of allergic mediators from the mast cells, basophils, eosinophils and/or ROS, RNS, proteases and other substances from T-cells will lead to a damage of tubular epithelial cells and basement membrane with development of inflammatory response and infiltration of the renal interstitium with inflammatory cells including macrophages that stimulate “proresolving” response with fibrosis. NSAIDs are the most frequently prescribed drugs, especially in aging patients. Both selective and non-selective NSAIDs suppress synthesis of prostaglandins in the kidneys thus leading to their ischemia. Side effects of therapy with NSAIDs affecting kidneys include acute kidney injury due to ischemia, acute hypersensitivity interstitial nephritis, acute interstitial nephritis, minimal change disease and membranous nephropathy.

Other causes of interstitial nephritis involve urate nephropathy, nephrocalcinosis (formation of calcium stones in hypercalcemia), acute phosphate nephropathy, light-chain cast nephropathy and bile cast nephropathy in hepatorenal syn-

drome.

Pathophysiological basis for treatment of interstitial nephritis are: (1) discontinuation of therapy with drug which induced interstitial nephritis; (2) short course of glucocorticoids to suppress excessive inflammatory response; (3) management of complications.

Acute renal failure (ARF)

Acute renal failure is a potentially reversible syndrome, which is characterized by a rapid fall of GFR, development of oliguria, accumulation of nitrogenous waste products, electrolyte and acid-base disorders. However, not all patients may develop oliguria. According with its etiology, ARF is classified into prerenal, renal and postrenal (Fig. 6-7):

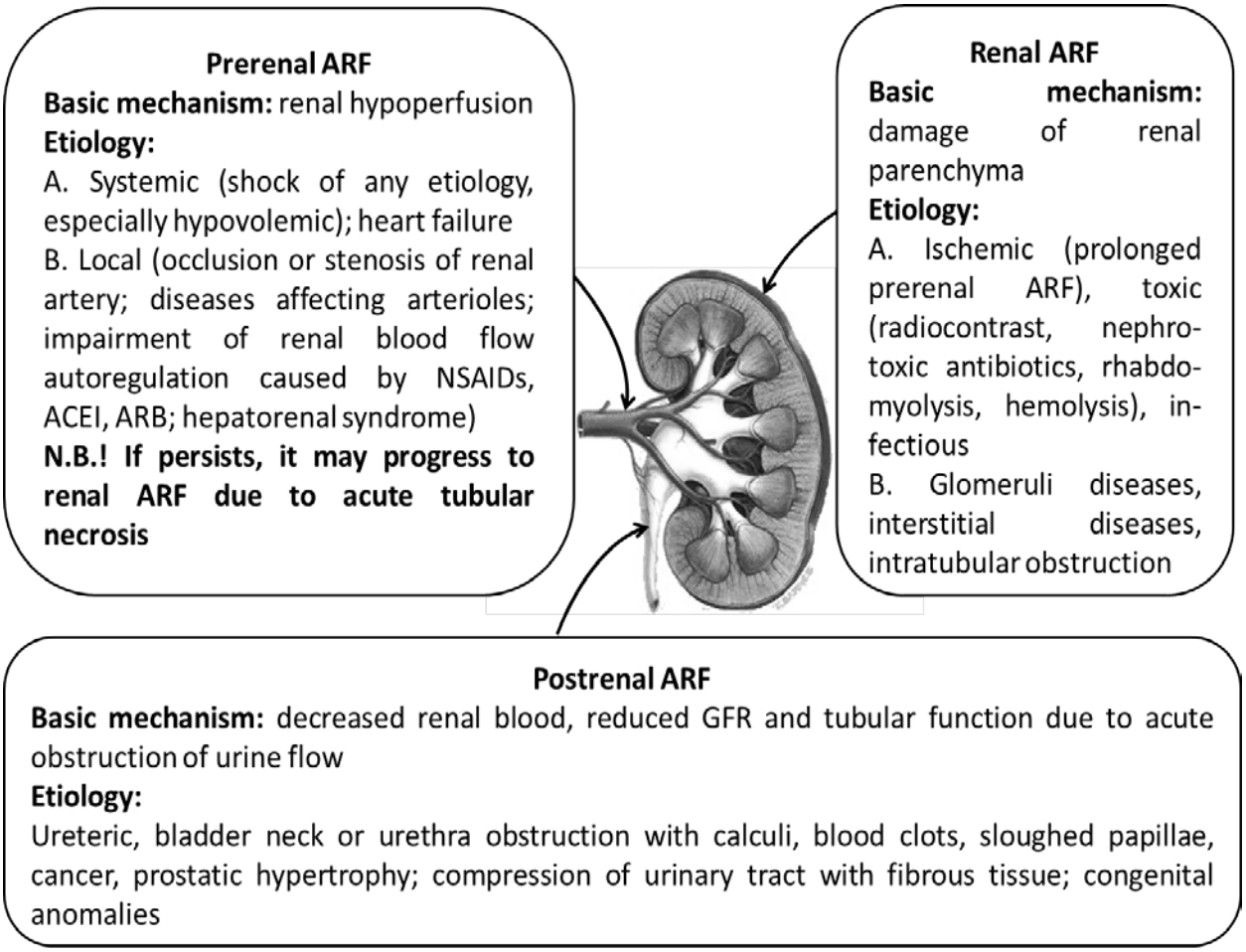


Figure 6-7. Etiology of acute renal failure

ACEI, Angiotensin Converting Enzyme Inhibitors; ARB, Angiotensin Receptor Blockers; ARF, Acute Renal Failure; GFR, Glomerular Filtration Rate; NSAIDs, Non-Steroidal Anti-Inflammatory Drugs

Basic event during ARF is a reduction of GFR. Normally it is determined by several factors (Fig. 6-8). GFR depends on the coefficient of filtration (K_f) and net

filtration pressure according with the formula:

$$GFR=K_f \times (HP_G - HP_{BC} - P_{onc\text{-}G} + P_{onc\text{-}BC}),$$

where HP_G is a hydrostatic pressure in the glomerulus, HP_{BC} is a hydrostatic pressure in the Bowman's capsule, $P_{onc\text{-}G}$ is a plasma oncotic pressure in the glomerulus and $P_{onc\text{-}BC}$ is a oncotic pressure in the Bowman's capsule, which is normally equal to approximately zero. Hence, reduction in the coefficient of filtration, increase of resistance of afferent arterioles (vasoconstriction), or decrease of resistance of efferent arterioles (vasodilation), or elevation of the plasma oncotic pressure, or rise of hydrostatic pressure in the Bowman's capsule followed by urine flow obstruction leads to fall of GFR. However, normally GFR is protected from severe fluctuations by two important mechanisms – autoregulation of renal blood flow and tubuloglomerular feedback mechanism. Owing to these mechanisms, GFR is supported in relatively stable level in a range of arterial blood pressure between 75 and 160 mm Hg.

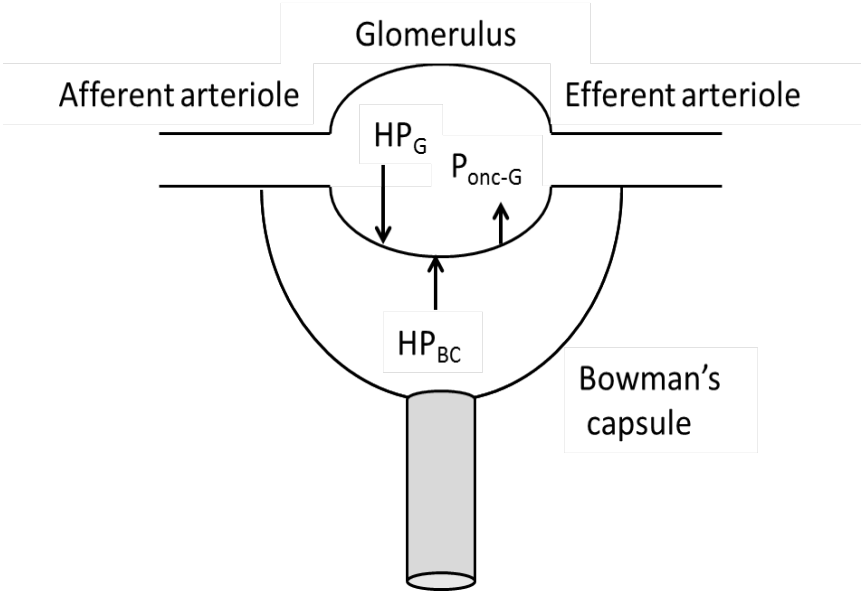


Figure 6-8. Forces driving glomerular filtration
(See explanation in the text)

It is important to know, than in some individuals with congenital or acquired oligonephropathy (due to reduced nephrons number) GFR is maintained or by vasodilation of afferent arterioles mediated by prostaglandins (prostacyclin, prostaglandin E_2), kinins, and nitric oxide or by slightly vasoconstriction of efferent arterioles provoked by angiotensin II. That is why use of NSAIDs, which inhibit cyclooxygenase activity and blunt synthesis of prostaglandins, may impair GFR thus leading to prerenal ARF. Similarly, inhibitors of angiotensin converting enzyme and angiotensin receptor blockers impair formation or action of angiotensin II, a potent vasoconstrictor of efferent glomerular arterioles with reduction of GFR.

Hypoperfusion of kidneys during prerenal ARF (See Fig. 6-7) leads to oliguria and elevated BUN with BUN-creatinine ratio more than 15:1 (which is termed

by “prerenal azotemia”). Because the medulla is the most sensitive to ischemia (where tubules are disposed), prolonged renal hypoperfusion, especially in case of preexisted oligonephropathy, may lead to the ischemic acute tubular necrosis (ATN). Universal molecular mechanisms including ATP deficiency, accumulation of intracellular Ca^{2+}, oxidative and nitrozative stress results in reversible, and after that – irreversible damage of tubular epithelial cells and their death from both necrosis and apoptosis. However, even before irreversible injury proximal tubular epithelial cells and epithelial cells of ascending limb of Henle loop lose their polarity, loss their brush border, redistribute integrins and Na^+/K^+-ATPase on the apical surface and desquamate forming casts. Together with fall of net filtration pressure as disequilibrium between afferent and efferent arteriole tone mediated by powerful sympathetic stimulation, RAAS activation and lack of endothelial vasodilators in hypovolemic condition, rise in hydrostatic pressure in the Bowman’s capsule due to casts formation result in the falling of GFR (Fig. 6-9).

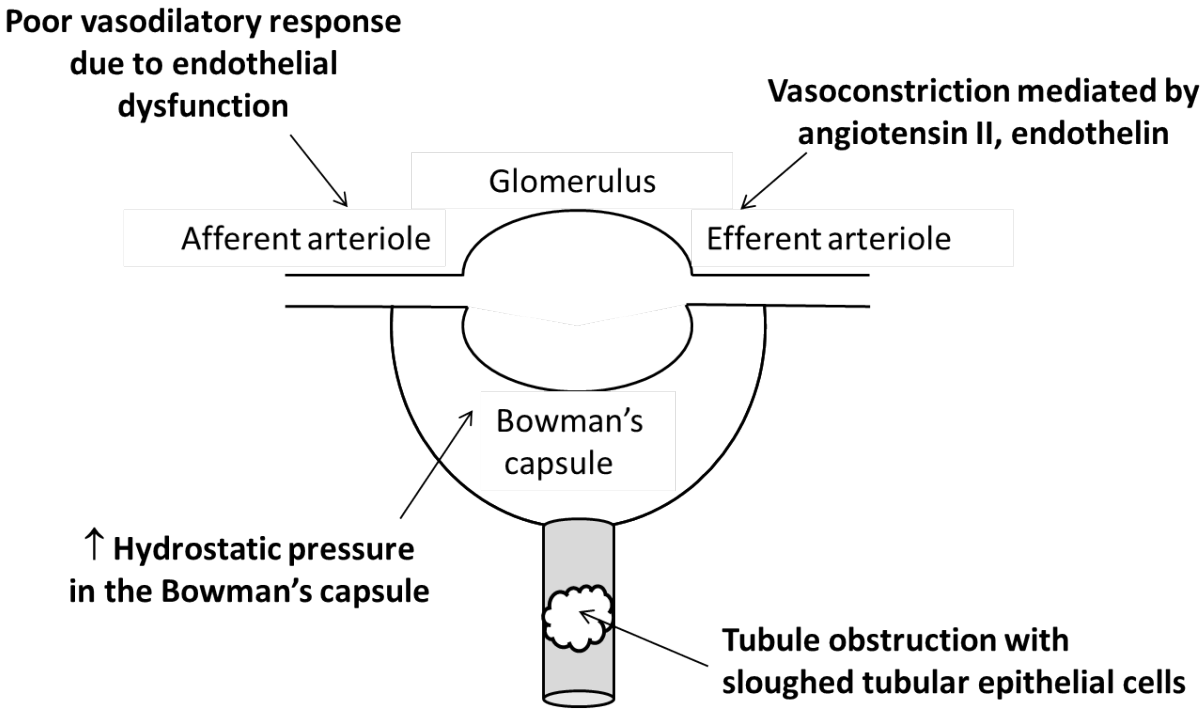


Figure 6-9. Mechanisms of GFR reduction during prerenal ARF

Clinically, ATN progresses following three stages (Table 6-3):

Table 6-3. Clinical course of ischemic ATN

Phases of acute renal failure	Pathogenesis	Clinical and laboratory symptoms
Initiating phase, lasting several hours or days	Circulatory collapse, renal hypoperfusion, ↓ GFR, ischemic acute tubular necrosis	Symptoms are resulted from underlying disorder

Maintenance phase, lasting several days	↓ GFR due to several mechanisms: (1) endothelial dysfunction and corresponding decrease in net filtration pressure; (2) compression of renal blood vessels with edema; (3) decrease in K_f caused by contraction of mesangial cells in response to hyperproduction of ET-1, PAF, TXA2, leukotrienes, Ang II; (4) contraction of afferent arterioles via tubuloglomerular feedback mechanism. Inadequate filtration and reabsorption lead to fluid retention, accumulation of waste products, and electrolyte disorders	Oliguria (however, nonoliguric ARF was detected during last decades), uremia (↑ BUN and creatinine+clinical symptoms), hyperkalemia, acidosis, edema, pulmonary congestion, muscle weakness, ECG changes, in severe cases – neuromuscular irritability, seizures, somnolence, coma and death, bleeding syndrome, secondary immunodeficiency
Recovery phase	Repair of renal tissue, gradual increase in renal output, relatively delayed restoration of renal tubular function (reabsorption) and improvement of concentrating ability	Polyuria, urine with low specific gravity, may develop dehydration, hypernatremia, hypokalemia, arrhythmia

Renal ARF is resulted from progressing diseases affecting renal parenchyma, prolonged ischemia and exposure of some exogenous or endogenous nephrotoxins. For example, exogenously injected radiocontrast agents, anti-inflammatory drugs cyclosporine and tacrolimus may lead to acute renal ARF in patients with preexisting chronic kidney disease. Radiocontrast agents provoke intrarenal vasoconstriction and oxidative stress with damage of tubular epithelial cells. However, radiocontrast nephropathy is a potentially reversible. Aminoglycoside antibiotics also may lead to renal ARF through direct toxic influence on the tubular epithelial cells with their sloughing and obstruction of renal tubules. Aminoglycoside-induced nephrotoxic ARF, as radiocontrast-induced ARF develop after several days of therapy or investigation, accordingly. Other drugs (antifungal amphotericin B, some anticancer drugs) also may induce nephrotoxic ARF.

Endogenous nephrotoxins include myoglobin, hemoglobin, urate, calcium, oxalate and paraproteins secreting by myeloma cells. Rhabdomyolysis is a relatively common cause of nephrotoxic ARF. Myoglobin released from skeletal muscles induces ROS formation with development of oxidative stress with irreversible injury of tubular epithelial cells with intratubular cast formation and leads to impaired bioavailability of NO resulting in vasoconstriction. Similar mechanisms are responsible for toxic ARF after hemolysis. Release of uric acids from dying leuke-

mic cells after chemotherapy ("tumor lysis syndrome") may lead to intratubular obstruction and fall of GFR. Light chains of immunoglobulins in patients with multiply myeloma also have direct toxic effects on the tubular epithelial cells.

Postrenal ARF is fewer form of ARF taking less than 5% of all causes. One-side obstruction of urine outflow is compensated by opposite unaffected kidney, and GFR is not falling significantly if nephrons number and structure are unchanged. In contrast, obstruction of urine outflow at the level of bladder neck (due to prostate enlargement), neurogenic bladder and after therapy with anticholinergic drugs may lead to postrenal ARF frequently. Obstruction of ureter with calculi, infiltration of ureter by tumor cells, external compression of ureters of bladder with scar, tumor or abscess also may lead to postrenal ARF. GFR doesn't fall significantly during first days after obstruction, but continued glomerular filtration enhances hydrostatic pressure upper to the sight of obstruction with distension of ureter, renal pelvices, and calyces (hydronephrosis), producing rise in hydrostatic pressure in the Bowman's capsule and fall in GFR. Renal blood flow also falls with increased risk of ischemic damage of tubular epithelial cells. Prolonged hydronephrosis may lead to atrophy of the kidney.

ARF may lead to several complications:

- Expansion of extracellular fluid volume and generalized edema and potentially life-threatening pulmonary edema. Such hypervolemia is resulted from decreased water and salt excretion during first stages of ARF.
- Electrolyte disorders:
  A. Hyperkalemia which is caused by following mechanisms: (1) reduced potassium excretion by kidneys; (2) release of K^+ from damaged tissues or cells during rhabdomyolysis, hemolysis or tumor lysis syndrome; (3) release of K^+ from cells under metabolic acidosis. Severe hyperkalemia may lead to arrhythmia.
  B. Hyponatremia is associated with excessive consumption of free water or administration of isotonic or hypotonic fluids. Hyponatremia may result in plasma hypoosmolality and cellular swelling. In severe cases intracellular brain edema may develop.
  C. Hyperphosphatemia, which is developed after fall of GFR and/or releasing from damaged tissues and cells. Hyperphosphatemia may lead to formation of calcium phosphate, and as a result to hypocalcemia.
  D. Hypocalcemia is explained by (1) formation of calcium phosphate and its deposition in damaged tissue; (2) resistance of tissues to parathormone; (3) deficiency of active form of vitamin D – 1,25-dihydroxyvitamin D. Severe hypocalcemia results in paresthesia, seizures, altered mental status and prolongation of QT interval on the ECG.
- Metabolic acidosis with elevated anion gap due to accumulation of non-volatile acids and their inadequate excretion.
- Accumulation of "uremic toxins" like as BUN, creatinine, creatine,

guanidine, methyl guanine, tryptophan, polyamines, phenols, cytokines, etc.

- Anemia, which is multifactorial, resulted from: (1) erythropoietin deficiency; (2) hemolysis; (3) hemodilution; (4) bleeding; (5) reduced survival time of RBCs.
- Bleeding syndrome due to thrombocytopenia, thrombocytopathia, deficiency of clotting factors and/or their dysfunction.
- Infectious complications, which are resulted from abnormal leukocytes function and deficiency of immunoglobulins.
- Vigorous diuresis leading to dehydration, hypernatremia, hypokalemia, hypomagnesaemia, hypocalcemia, hypophosphatemia.

Pathophysiological basis for management of ARF: (1) adequate prevention, for example, adequate treatment of shock, avoidance of nephrotoxic agents in patients having preexisted renal diseases, correct management of tumor lysis syndrome in leukemic patients; (2) treatment of specific form of ARF: a) in prerenal ARF adequate correction of hypovolemia, management of serum potassium and acid-base equilibrium, correction of heart failure and complications; b) in renal ARF treatment depends on etiology and include aggressive anti-inflammatory therapy of glomerulonephritis; in ischemic ATN – to restore systemic hemodynamics and renal perfusion with volume resuscitation and vasopressors; in nephrotoxic ARF – to eliminate nephrotoxins, to induce alkaline diuresis for rhabdomyolysis, to administer allopurinol in tumor lysis syndrome; c) in postrenal ARF percutaneous catheterization or ureteric state during ureteric obstruction, administration of intravenous saline to maintain blood pressure in the polyuric state; (3) management of complications: salt and water restriction, diuretics and ultrafiltration to reduce expanded intravascular volume; restriction of dietary potassium intake, loop diuretics to induce potassium excretion, glucose and insulin to promote intracellular potassium handling to reduce hyperkalemia; sodium bicarbonate to alleviate metabolic acidosis; restriction of dietary phosphorus intake and administration of calcium carbonate or acetate to reduce hyperphosphatemia; calcium carbonate or gluconate to decrease hypocalcemia; avoidance of other nephrotoxins including drugs. Hemodialysis is a useful method to support renal function until renal recovery appears.

Chronic kidney disease and chronic renal failure

Chronic kidney disease (CKD) is a pathophysiological process, which is initiated by different causes, that results in the permanent loss of nephrons number and a gradually decrease of kidney function. The National Kidney Foundation Practice Guidelines, 2002, has proposed the following classification of CKD (Table 6-4). This classification is based on estimated GFR (eGFR).

Table 6-4. Classification of CKD

	Stage	Characteristic	Estimated GFR, ml/min/1.73 m^2	
	1st	Normal or even increased eGFR despite kidney damage	≥90	
	2nd	Mild decline in GFR	60-89	
Chronic renal failure	3rd	Moderate decrease in GFR	30-59	
	4th	Severe decrease in GFR	15-29	
	5th	Kidney failure	<15 or dialysis	ESRD

Chronic renal failure is a progressing significantly irreversible reduction of nephron number and fall in eGFR below 60 ml/min/1.73 m^2. It includes 3-5 stages of CKD according with above-mentioned classification. End Stage Renal Disease (ESRD) is a 5th stage of CKD with uremic syndrome. Uremia is defined as a clinical and laboratory syndrome, which is characterized by elevated concentration of nitrogenous waste products in the blood serum (usually detected BUN and creatinine) and clinical features of intoxication with waste products. Uremic syndrome will be discussed further.

Etiologically CKD is caused by different diseases affecting renal parenchyma, but now is commonly resulted from diabetes mellitus, arterial hypertension and glomerulonephritis. Other diseases including inborn anomalies, especially autosomal dominant polycystic kidney disease, obstructive diseases affecting urine outflow, tubulointerstitial diseases and vascular diseases affecting kidneys are less common causes of CKD. Natural history of CKD development is illustrated in the Fig. 6-10.

Once appeared, renal diseases affecting nephrons, initiates death of nephron cells. However, genetic predisposition and adverse intrauterine events (prenatal stress, maternal diseases, maternal undernutrition or overeating, drugs, pernicious habits, intrauterine growth retardation, prematurity, etc.) through genetic and epigenetic events according with theory of a “thrifty phenotype” result in impairment of nephrogenesis and reduction in nephron number even in newborns. Renal diseases and concomitant diseases affecting individual during childhood or adulthood (arterial hypertension, heart failure, systemic diseases affecting kidneys, amyloidosis, metabolic diseases and many others) cause renal injury, inflammation and glomerulosclerosis. As a result, nephron number decreases with time. However, compensatory hyperfiltration occurs and even reduced nephron number up to 50% compared with normal doesn’t associate with reduction in GFR. This fact explains why healthy individual may donate one kidney for transplantation without significant deterioration of GFR. Nevertheless, prolonged hyperfiltration supports progressing and damage of nephrons with decrease in their number. Progressive injury of nephrons triggers and supports of inflammatory response that recruits of leuko-

cytes and proinflammatory mediators locally in the site of inflammation. ROS, RNS, proteases, complement, and proinflammatory cytokines cause secondary injury with switching of inflammatory response to proresolving response later. Polarization of macrophages from M1 to M2 phenotype, synthesis of anti-inflammatory cytokines and epithelial-mesenchymal transition are key factors leading to fibrosis, further reduction in nephron number and corresponding decrease in GFR.

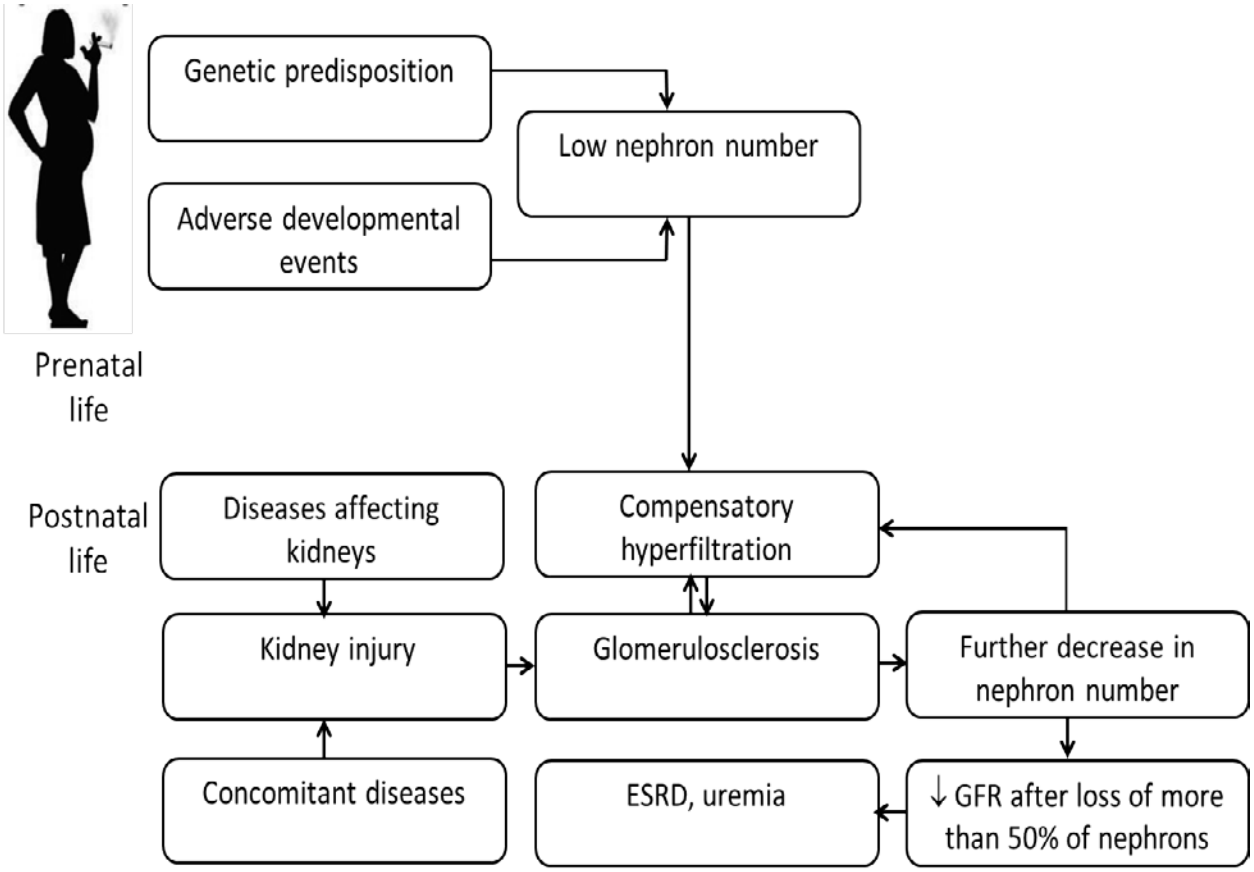


Figure 6-10. Natural history of CKD

Uremia

Loss of at least 50% of the initial nephron number results in fall of GFR and development of uremic syndrome. This syndrome is characterized by accumulation of blood urea nitrogen, uremic toxins, metabolic disorders and polyorgan abnormalities. Chronic dialysis may relieve these abnormalities only partially, that is why transplantation of the human kidney is thought to be a choice in the management of chronic renal failure and uremia.

Manifestations of the uremic syndrome are schematically illustrated in the Fig. 6-11.

Basic pathogenetic mechanisms of uremia are:

- Loss of normal kidney functions;
- Accumulation of hundreds of so-called “uremic toxins”, which are both water-soluble and insoluble, protein-bound, charged or uncharged substanc-

es. They include guanidine compounds, salts of uric acid, hippurates, products of DNA and RNA metabolism, phenols, indols, polyamines, myoinositol, benzoates and "middle molecules" (compounds with molecular mass varying from 500 to 1500 Da.

- Impairment of fluid, electrolyte and acid-base equilibrium;
- Progressive vascular and metabolic complications;
- Progressive systemic inflammation which is proved by elevated acute phase proteins.

Mechanisms of manifestations of uremia are summarized in the Table 6-5.

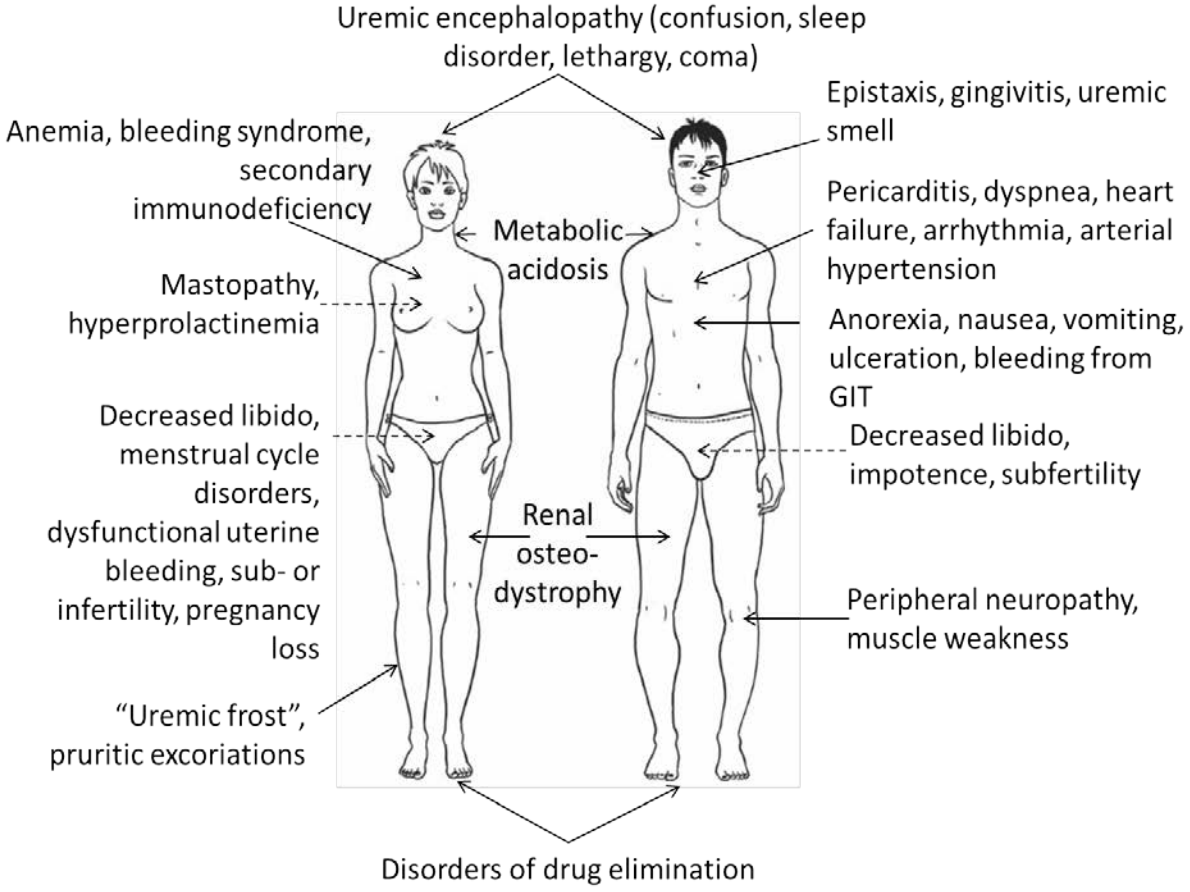


Figure 6-11. Common symptoms of uremia

Solid arrows indicate common symptoms for affected males and females; dashed arrows indicate sex-specific features.

Table 6-5. Pathogenesis of uremia-associated symptoms

Symptom	Pathogenesis / *Pathophysiological basis for management*
Uremic encephalopathy, peripheral neuropathy	(1) Toxic effects of uremic toxins (creatinine, guanidine, guanidinosuccinic acid, methylguanidine, etc.) on the brain regions that are responsible for cognition including thalamus, mammillary bodies, cerebral cortex with excitation of receptors to the N-methyl-D-aspartate (NMDA) receptors and inhibition of A-

	type receptors to gamma-aminobutyric acid (GABA); (2) Oxidative and nitrozative-stress-mediated damage of neurons with their apoptosis, necrosis, or autophagy; (3) Accumulation of Ca^{2+} in the brain cortex and calcium-mediated injury of neurons; (4) Intracellular edema of neurons due to suppression of Na^{+}/K^{+} ATPase activity by uremic toxins and electrolyte disorders; (5) Damage of neurons due to brain hypoperfusion, which is resulted from vascular abnormalities due to secondary arterial hypertension; (6) Atrophy and demyelination of nerve endings induced by uremic toxins. *No any specific therapy; restriction of dietary proteins, dialysis and renal transplantation are indicated*.
Volume expansion, electrolyte disorders	Reduction of GFR and activation of RAAS lead to volume expansion and Na^{+} retention with arterial hypertension, however, during late stages of CKD patient may develop hyponatremia due to excessive water ingestion. Loss of ability to keep water and sudden dehydration following diarrhea, vomiting, sweating may lead to vascular collapse or even shock. Loss of eGFR below than 5 ml/min/1.73 m^2 results in hyperkalemia due to fall of aldosterone-mediated potassium transport in distal tubules. Bidirectional disorders of potassium homeostasis may be induced by K^{+} sparring or thiazide diuretics, ACE inhibitors, angiotensin II receptor blockers, and β-blockers. Hyperkalemia also is induced by excessive protein catabolism, hemolysis, internal bleeding, blood transfusions, and metabolic acidosis. Hypokalemia is less common. *Correction of dietary salt intake; loop diuretics; dietary restriction of potassium; avoidance of potassium-retaining drugs.*
Metabolic acidosis	(1) Loss of ammonia production and poor protons excretion; (2) Hyperkalemia-induced suppression of ammonia production; (3) Impairment of sodium and bicarbonate reabsorption; (4) Corresponding renal tubular acidosis type 4. *Alkali supplementation (sodium bicarbonate)*.
Disorders of calcium and phosphorus homeostasis; bone disease	Impairment of phosphate excretion corresponding with deterioration of urine excretion leads to hyperphosphatemia. Hyperphosphatemia results in combination of Ca^{2+} with phosphates and hypocalcemia. Hypocalcemia and hyperphosphatemia stimulate releasing of parathyroid hormone (PTH), which in

	turn, activates and calcium releasing from bone tissue. The latter may to vascular and heart calcification, increase in vascular stiffness and peripheral vascular diseases and myocardial fibrosis progression. Moreover, PTH stimulates bone turnover with formation of bone cysts, bone pain, and increases bone fragility. Next, kidney is a source of vitamin D hydroxylation. Defect in $1,25(OH)_2D_3$ formation results in poor calcium absorption in the gut, excessive loss of calcium with urine and insufficient mineralization of bone tissue and poor osteoblasts differentiation with osteomalacia. Osteomalacia is caused also by aluminum toxicity after use of imperfect dialysate solutions. Adynamic bone disease, especially in patients with diabetes mellitus, is characterized by reduced bone volume due to low turnover of bone modeling and remodeling processes and delayed mineralization, which is resulted from excessive suppression of PTH release by excessive doses of vitamin D. Metabolic acidosis stimulates dissolution of bone buffers thus leading to bone decalcification and osteoporosis. Recently additional mechanism of bone disease during uremia was proposed, namely deficiency of Klotho protein. It is secreted by multiply cells, but especially in high levels by epithelial cells in distal convoluted tubules. The protein exists at membrane-bound and plasma-soluble form. Klotho protein possesses multiply functions through endocrine, paracrine and autocrine action involving regulation of cellular aging (protein was named in the honest of Zeus' daughter Klotho, which spinning the thread of life in Greek mythology), antioxidative protection, insulin sensitivity, control of PTH action and $1,25(OH)_2D_3$ production, RAAS suppression, energy formation, and regulation of ions transport. Deficiency of plasma Klotho protein in patients with CKD and uremia associates with multiply adverse effects including CKD progression, secondary hyperparathyroidism, vascular calcification and cardiac hypertrophy. *Low phosphate diet; phosphate-binding agents (calcium acetate, calcium carbonate, non-calcium containing polymers); vitamin D3 or it analogs; calcimimetic agents; supplementation of exogenous Klotho and/or up-regulation of endogenous Klotho production by ACE inhibitors, HMG CoA reductase inhibitors (statins), vitamin D analogues, PPAR-γ agonists, antioxidants.*
Cardiovascular abnormalities	Secondary arterial hypertension is resulted from: (1) volume expansion; (2) RAAS activation; (3) endothelial dysfunction and vascular stiffness; (4) lack of prostaglandins production in

	the kidneys. CKD and uremia accelerate progression of CHD by the following mechanisms including endothelial dysfunction, systemic inflammation, hyperlipidemia, vascular calcifications and coexisting pathologies. Electrolyte disorders, metabolic acidosis, fibrosis and myocardial remodeling increase risk of arrhythmias. That is why CHD is a common cause of death among uremic patients. Heart failure may be systolic, diastolic or both. It is resulted from volume and/or pressure overload, myocardial remodeling, and systemic inflammation. Coexisting anemia stimulates RAAS thus enhancing volume overload. *Lifestyle changes; salt restriction; diuretics; ACE inhibitors; angiotensin II receptor antagonists; HMG CoA reductase inhibitors (statins), prevention or correction of hyperhomocysteinemia with folates supplementation*.
Polyserositis	Uremic pericarditis, pleuritis and pleural effusion are caused by releasing of uremic toxins by serous membranes; corresponding immunodeficiency predisposes to contamination and infectious inflammation. *Dialysis; treatment of infections.*
Hematologic disorders	Pathogenesis of anemia is illustrated in the Fig. 1-7. Bleeding syndrome is resulted from: (1) abnormal platelets functions; (2) lack of coagulation factors; (3) increased in vascular permeability after exposure of uremic toxins. However, patients with nephrotic syndrome are prone to thromboembolic complications (See Fig. 6-4). Secondary immunodeficiency is explained by leukocytes (mainly lymphocytes) suppression by uremic toxins. Dialysis and use of immunosuppressive drugs after kidney transplantation are also important mechanisms of secondary immunodeficiency. *Recombinant erythropoietin therapy for the control of anemia.* *Desmopressin, cryoprecipitate, blood transfusions and dialysis are indicated for the correction of bleeding syndrome.* *Warfarin is recommended to prevent thromboembolic complications in patients with thrombophilia*.
Gastrointestinal abnormalities	Uremic fetor is a result of degradation of urea to ammonia in saliva. Uremic toxins also lead to anorexia, nausea and vomiting. Excretion of uremic toxins through mucosa induces gastritis and ulceration in any part of the GIT. *Protein restriction; antacids; proton pump inhibitors; dialysis.*
Endocrine disturbances	Abnormal formation, binding and degradation of sex hormones lead to hypogonadism in both sexes and sexual disorders. Poor degradation of insulin, astonished glycogen store in the kid-

	neys and impaired sensitivity to insulin may result in abnormal metabolism. *No any specific therapy; dialysis and renal transplantation are indicated.*
Dermatologic abnormalities	Release of uremic toxins through skin leads to decrease in sweat and sebaceous glands number. As a result, skin is dry with typical "uremic frost". Crystals of urea and phosphates provoke pruritus with increased risk of infection. *Dialysis; local moisturizers; topical glucocorticoids; oral antihistamines; ultraviolet radiation.*
Impairment of drug elimination	(1) Hypoalbuminemia accelerates metabolism of free, unbounded with albumin portion of drugs; (2) Slowing of metabolic degradation of some drugs; (3) Some drugs contain nitrogen, sodium, potassium, magnesium thus potentiating electrolyte disorders; (4) Phosphate-buffering antacids, which are indicated to control hyperphosphatemia and hypocalcemia, impair absorption of some drugs. *Monitoring; avoidance of nephrotoxic drugs and drugs impairing metabolic characteristics.*

Urolithiasis (urinary stone disease)

Urinary stone disease is a multifactorial disease which is characterized by the formation or presence of concretions in the urinary tract. The prevalence of the disease has steadily increased during last decades. It is explained by lifestyle changes, changes in diet, increasing incidence of obesity, diabetes mellitus, and even global warming. Moreover, nephrolithiasis currently is thought to be a systemic disease, which is strongly related to other pathologies such as coronary heart disease, CKD and ESRD, osteoporosis with increased risk of fractures, aortic calcification, arterial hypertension, diabetes mellitus, gout, metabolic syndrome, sarcoidosis, bowel diseases and intake of some drugs.

The process of concretions formation in the urinary tract has been explained by several pathophysiological mechanisms. Urine is a unique complex solution of various solutes with different solubility. The kidneys must conserve water and excrete substances with low solubility. When the urine becomes hypersaturated due to accumulation of insoluble substances, crystals formation and growth are activated. Schematically representation of pathogenesis of urinary stones formation is illustrated in the Fig. 6-12. There are several types of stones: calcium stones, uric acid stones, cysteine stones, struvite stones, and mixed stones. Calcium oxalate, calcium phosphate and uric acid stones are most common at present.

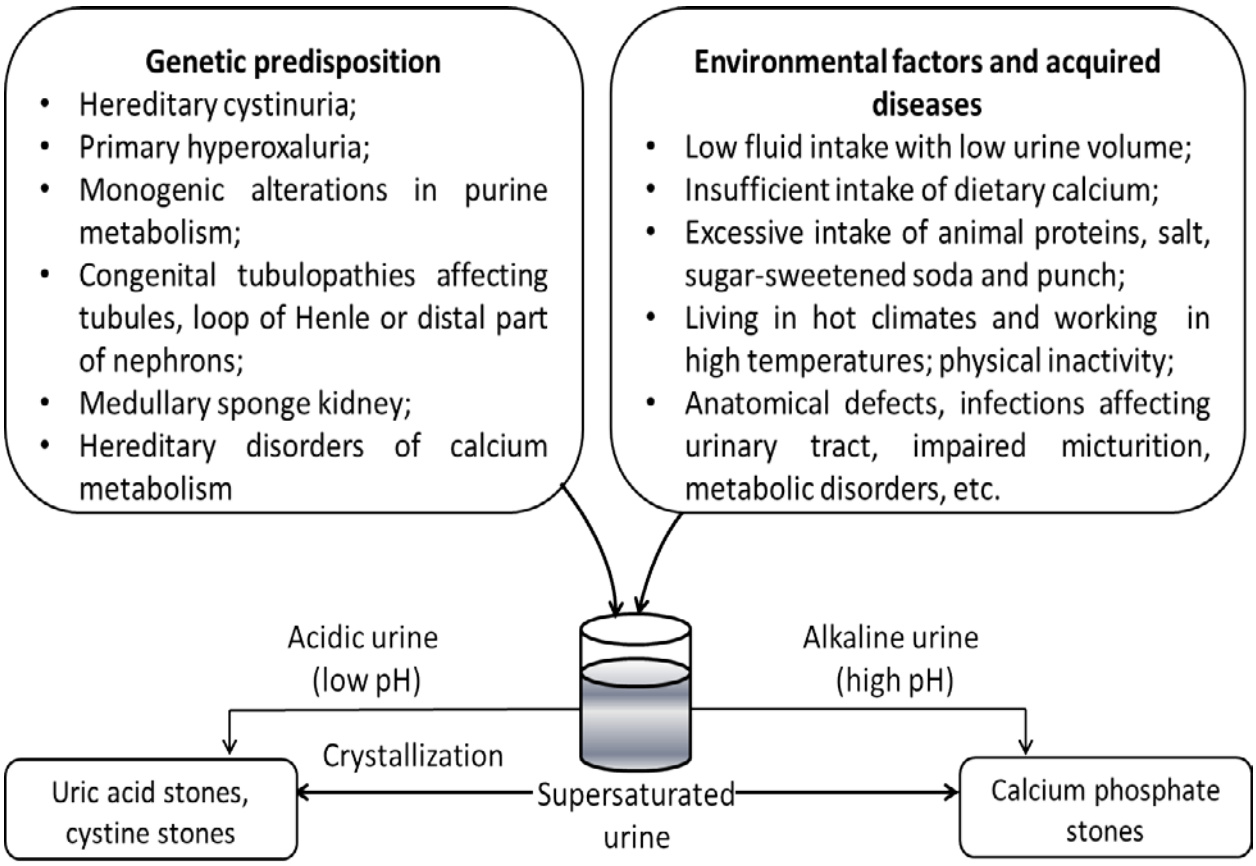


Figure 6-12. Simplified pathogenesis of urinary concretions formation

Crystals containing above mentioned substances might get trapped in the tubular lumen and begin the process of stone formation. Two theories try to explain this process. According with the theory of free particles, crystals aggregate free in the tubular lumen. Another, fixed particle theory postulates that crystal growth starts from plaques of calcium phosphate (Randall's plaques) in the interstitium within renal papillae. These plaques may originate from the basement membrane of the Henle loop or from the basement membrane of collecting tubules and vasa recta. However, inhibitors of crystallization may impair process of stone formation. For example, inorganic pyrophosphate delays formation of calcium phosphate stones; magnesium, citrate and glycoproteins inhibit calcium oxalates crystallization. Urinary citrate has several mechanisms of protection from stones formation: chelating calcium, inhibiting nucleation and crystallization by interacting with Tamm-Horsfall protein. Other inhibitors of stone formation are osteopontin, pyrophosphate, bisphosphonates, protein nephrocalcin and mucopolysaccharides. Disbalance in the system "promoters of crystallization / inhibitors of crystallization" and low urine volume might lead to stones formation and progression.

Particular features of different urinary stones, mechanisms of their formation and backgrounds for prevention and treatment are discussed further.

Calcium stones (consisting from calcium oxalate and calcium phosphate) predominate in males. Main risk factors include elevation in concentration of cal-

cium and phosphates and decrease in concentration of citrate. Excessive excretion of calcium by kidneys is detected in familial idiopathic hypercalciuria, primary hyperparathyroidism, sarcoidosis, prolonged immobilization and different bone disease and after use of some drugs (loop diuretics). Moreover, sodium intake also influences hypercalciuria. Normally calcium is reabsorbed in the proximal tubules passively via the concentration gradient maintained by active reabsorption of sodium. Excessive NaCl intake leads to volume expansion, decrease in proximal Na^+ and Ca^{2+} reabsorption and increase in Ca^{2+} excretion. Calcium stones formation is also associated with hyperuricosuria, hyperphosphatemia and hyperoxalaturia.

Uric acid stones are more common in males, they often associate with gout. Hyperuricosuria is a hallmark of high dietary purines intake, high cell turnover (in myeloproliferative disorders, chemotherapy of malignant tumors and Lesh-Nyhan syndrome (See Part XI in the Textbook "General pathophysiology: the essentials"). When urine pH is low, elevated concentration of uric acid increases urine supersaturation. Low urine pH is seen in individuals with high animal protein consumption, because of animal protein has a higher content of sulfur and creates more significant acid load than vegetable protein. Insulin resistance may also produce low urine pH due to impairment of ammonia excretion and urine acidification. Chronic diarrhea due to loss of bicarbonates acidifies urine too.

Oxalate stones are due to hyperoxaluria. It is resulted from:

- Dietary overconsumption of high-oxalate foods (spinach, nuts, legumes, chocolate);
- Low calcium diet (because of low calcium intake associates with stimulation of intestinal absorption of oxalate and high oxalate urinary excretion);
- Diseases of gastrointestinal tract and pancreas with fat malabsorption (calcium in the bowel lumen binds with fats instead of oxalate and oxalate can't absorb in the colon → unabsorbed fatty acids together with bile salts in the colon damage intestinal epithelial cells → enhanced oxalate absorption);
- Primary hyperoxaluria, which is rare autosomal recessive disorder.

Cystine stones are relatively uncommon. Their formation is resulted from cystinuria, which is a hereditary disorder. Mutated gene encodes a dibasic amino acid transporter (cysteine, lysine, arginine and ornithine) by the brush border of renal tubular and intestinal epithelial cells. As a result, individuals release more above-mentioned amino acids with urine. Low urine pH facilitates cystine stone formation.

Struvite stones are relatively common and potentially dangerous. Struvite stones are formed in individuals, who regularly are exposed by invasive manipulations in the urinary tract (for example, bladder catheterization). These manipulations facilitate bacterial overgrowth, and bacteria, especially Proteus species having urease activity, convert urea to CO_2 and NH_3; further the former is hydrolyzed to NH_4^+. Next, several important chemical reactions in the urine may occur:

$$CO_2+H_2O \rightarrow H_2CO_3 \rightarrow 2H^+ + CO_3^-$$

$CO_3^{-}+Ca^{2+} \rightarrow CaCO_3$ (calcium carbonate formation)

$NH_4^{+}+PO_4^{3-}+Mg^{2+} \rightarrow MgNH_4PO_4$

(magnesium ammonium phosphate, or struvite formation)

As a result, calcium carbonate admixes with struvite with formation of relatively large rectangular prisms which filling renal pelvis and calyces ("staghorn" phenomenon).

If stones begin to growth in the renal papillae and within the collecting duct, they are usually asymptomatic. Stones become symptomatic when they obstruct the uretereopelvic junction or ureter. This obstruction or stone passage produces severe flank or abdominal pain, sometimes vomiting, hematuria, dysuria and sometimes – oliguria. Mechanism of visceral pain in renal colic is following: obstruction of urine outflow → rise in pressure in the renal pelvis → distention of fibrous renal capsule → irritation of nerve endings → transmission of impulses through mesenteric and solar nerve plexus → pain processing in the posterior central gyrus, reticular formation, corresponding zones of the midbrain and interbrain. Impaired microcirculation in the affected kidney results in hypoxia, and accumulation of metabolites which are also able to cause irritation of nerve endings. Distal ureteral stones with diameter smaller than 5 mm may pass spontaneously, whereas larger stones may obstruct urinary tract.

Complications of urolithiasis include postrenal acute renal failure with azotemia, secondary infections of urinary tract, hydronephrosis, chronic kidney disease, secondary (renal) arterial hypertension and erythrocytosis due to EPO hyperproduction.

Pathophysiological basis for urinary stones prevention and treatment are following: (1) increase fluid intake to achieve a diurnal diuresis at least 2.5 L (this approach is recommended for prevention of all types of urinary stones) and cessation of carbonated drinks; (2) limit sodium intake; (3) limit oxalate-rich food; (4) increase consumption of fruits and vegetables and limit animal protein; (5) to maintain normal (not low) dietary calcium intake and to restrict vitamin C consumption to limit calcium oxalate stones formation; (6) thiazide diuretics which stimulate proximal sodium and passive calcium reabsorption thus decreasing hypercalciuria; (6) potassium citrate to alkalize urine to the optimal pH in recurrent calcium stones, uric acid and cystine stones formation; (7) allopurinol, which inhibits de novo purine synthesis, is recommended as second-line therapy of recurrent uric acid lithiasis; (8) thiol-containing drugs (like as D-penicillamine or captopril) to form soluble disulfide cysteine-drug complexes in cystine stones; (9) antimicrobial therapy and surgical removal of stones is the "gold standard" of struvite stones management; (10) treatment of renal colic: adequate analgesia, dilation of ureters, invasive restoration of urine outflow (nephrostomy, ureterostomy, or uretheral, urethral, or suprapubic catheterization), antibacterial therapy; (11) surgical or invasive (for example, extracorporeal shock-wave lithotripsy with placement of ureteral stent) treatment to remove stones according with indications.

Cystic kidney disease

It is a heterogeneous group of diseases including polycystic kidney diseases, acquired cystic kidney disease, medullary cystic renal diseases and some rare systemic diseases, which are characterized by renal cysts formation as accessory symptoms. Morphologically, renal cysts are sacs with walls consisting from a single layer of epithelial cells, and these sacs are filled with fluid. When such renal cyst is single and no any pathology is detected, the cyst is thought to be a simple cyst. The polycystic kidney diseases (PKDs) include hereditary disorders with different type of inheritance (autosomal dominant or autosomal recessive) which are characterized by the presence of bilateral expanding multiply renal cysts.

Autosomal dominant polycystic kidney disease (ADPKD) is a most common monogenic disease affecting humans (incidence varies from 1:400 to 1:1000) with 100% penetrance by age 90 years. The genetic backgrounds of the disease are mutations of TSC2 gene on chromosome 16 or PKD2 gene on chromosome 4. These genes normally encode proteins polycystins, which are responsible for cell-cell and cell-matrix adhesions and signal transduction. Generally, normal polycystins maintain normal structure of epithelial and endothelial cells. Mutations of above-mentioned genes result in abnormal structure and functions of polycystins with focal dilation and evagination of renal tubules. Tubular dilation is a result of alterations in extracellular matrix, focal hyperproliferation and excessive apoptosis of tubular epithelial cells, which must to occur up to thousand times in at least 1% of nephrons to cyst formation. Abnormal secretion of Na^+ and Cl^- by tubular epithelial cells results in cyst initiation and expansion. Excessive fibrosis and obliteration of nephrons occur in parallel with cysts expansion with development of ESRD in the future. ADCKD may manifest at any age, but most commonly during 3^{rd} of 4^{th} decades of life by renomegaly, urinary concentration defects displaying by nocturia, recurrent urinary tract infections, and secondary renal arterial hypertension. ADCKD may have extrarenal abnormalities: cerebral aneurysms, mitral valve prolapse and cysts in the parenchymatous organs including liver, pancreas, spleen, brain, ovaries and testis. There is no any specific strategy for prevention of cysts formation now. Management of ADCKD is based on the treatment and prevention of complications.

Autosomal recessive polycystic kidney disease (ARPKD) is a most severe disorder than ADPKD, but a relatively rare. It affects children and even neonates; ESRD is developed up to age 20 years. ARPKD is resulted from mutations of PKHD1 gene on chromosome 6. The gene encodes protein fibrocystin (polyductin) which is responsible for cellular adhesion and proliferation. This protein normally present in the distal tubules and collecting ducts in the kidneys, as in the pancreas, lung, and liver. That is why ARPKD may manifest even in utero by oligohydramnios and pulmonary hypoplasia. In children tubular dysfunction is characterized by polyuria, enuresis, and hyponatremia and hyperchloremic metabolic acidosis in association with hepatic fibrosis and portal hypertension, pancreatic fibrosis, respira-

tory failure, secondary renal arterial hypertension and recurrent infections affecting urinary tract. As with ADPKD, there are no specific approaches for prevention and treatment of ARPKD.

Acquired cystic renal disease affects individuals with ESRD on dialysis and usually is asymptomatic.

Medullary cystic kidney diseases are hereditary disorders due to gene mutations affecting proteins nephrocystins and uromodulin. These proteins are responsible for cellular adhesion and signal transduction. Affected individuals will have tubular dysfunction, hematuria, electrolyte disorders, recurrent urinary stones and sometimes extrarenal abnormalities.

Vascular disorders of the kidney

Different pathological processes (thrombosis, atherosclerosis, emboli, inflammation or arterial hypertension) may affect renal vessels. Depending on the type of affected blood vessels, vascular disorders of kidneys can be classified into diseases affecting renal arteries, veins, arterioles and microvasculature. These disorders also can be classified into acute (for example, in renal artery thrombosis or in hemolytic-uremic syndrome and thrombotic thrombocytopenic purpura) or chronic (in arterial hypertension, systemic diseases of connective tissue). Such disorders are manifested by abnormalities in the urinalysis, diary diuresis, azotemia, secondary renal arterial hypertension and uremia as a result of ESRD. These disorders were described in details in the appropriate parts of the present Textbook.

PART VII. PATHOPHYSIOLOGY OF THE ENDOCRINE SYSTEM

Hormones (from Greek "hormone" means "to stir up") are chemical messengers, produced by endocrine glands or endocrine cells (Table 7-1) in response to different biochemical or physiological stimuli, and are released into the blood, and affect distant organs and tissues in a regulatory manner by activation of specialized receptors.

Table 7-1. Short overview of the most important hormones

Endocrine glands	Hormones, site of production	Chemical structure	Main effects
Hypothalamus	Growth hormone-releasing hormone (GHRH)	Peptide	↑ of the growth hormone (GH) release from the anterior pituitary
	Somatostatin	Peptide	↓ of the GH release from the anterior pituitary
	Corticotropin-releasing hormone (CRH)	Peptide	↑ of the adrenocorticotropic hormone (ACTH) release from the anterior pituitary
	Thyrotropin-releasing hormone (TRH)	Peptide	↑ of the thyrotropin (TSH) release from the anterior pituitary
	Gonadotropin-releasing hormone (GnRH)	Peptide	↑ of the follicle stimulating hormone (FSH) and luteinizing hormone (LH) release from the anterior pituitary
	Antidiuretic hormone (ADH, vasopressin) is released from the posterior pituitary	Peptide	↑ of water reabsorption in the renal collecting tubules; peripheral vasoconstriction
	Oxytocin is released from the posterior pituitary	Peptide	Contraction the uterus during parturition; smooth muscle contraction of the milk breast ducts during breast feeding
Pituitary gland	Growth hormone (anterior pituitary)	Peptide	↑ of Insulin-like Growth Factor (IGF) secretion in the liver, ↑ synthesis of proteins, ↑ of cellular proliferation and linear growth; ↑ of insulin secretion; ↑ lipid catabolism, ↓ carbohydrates catabolism

	Prolactin (anterior pituitary)	Peptide	↑ of milk secretion
	Adrenocorticotropic hormone (anterior pituitary)	Peptide	↑ of glucocorticoids, and in the less extent – mineralocorticoids and androgens production in the adrenal cortex
	Thyrotropin (anterior pituitary)	Peptide	↑ of the T_3 (triiodothyronine) and T_4 (thyroxine) secretion by the thyroid gland
	Follicle stimulating hormone (anterior pituitary)	Peptide	Females: folliculogenesis in the ovary, ↑ of estrogens secretion Males: spermatogenesis
	Luteinizing hormone (anterior pituitary)	Peptide	Females: ovulation, control of development of corpus luteum of the ovary, ↑ of the progesterone and estrogens secretion by the corpus luteum of the ovary Males: ↑ of the testosterone secretion
	Melanocyte-stimulating hormone (intermediate lobe of hypophysis)	Peptide	Melanogenesis, skin pigmentation
Pineal gland	Melatonin	Amine	Regulation of circadian rhythms and secretion of hypothalamic hormones, sleep, mood, sexual maturation, reproduction, aging, antioxidant effects, regulation of immunity
Adrenal glands	Glucocorticoids: cortisol (zona fasciculata) and corticosterone (zonae fasciculate and glomerulosa) in the adrenal cortex	Steroids	Adaptation to stress, ↑ of the gluconeogenesis, anti-inflammatory action
	Mineralocorticoids: aldosterone (zona glomeruloza); corticosterone and 11-deoxycorticosterone have less mineralocorticoid activity. Produced in the in the adrenal cortex	Steroids	Sodium and water retention; loss of potassium
	Androgens: dehydroepi-	Steroids	Substrate of aromatase reaction; con-

	androsterone, dehydroepiandrosterone sulfate (DHEA, DHEAS, accordingly), androstenedione and small concentrations of testosterone (zonae fasciculate and reticularis) in the adrenal cortex		trol of secondary sexual characteristics, stimulation of axillar and pubic hair growth
	Catecholamines (epinephrine, norepinephrine) produced in the adrenal medulla	Amines	Acute stress response ("fright or fight response"), regulation of the myocardial contractility and vascular tone; glycogenolysis, gluconeogenesis, lipolysis
Thyroid gland	Triiodothyronine (T_3), thyroxine (T_4)	Amines	↑ of the metabolic rate; development of fetus, potentiation of catecholamines action on the heart
	Calcitonin	Peptide	Decrease in the Ca^{2+} concentration in the blood; ↓ of bone resorption
Parathyroid gland	Parathormone (PTH)	Peptide	Increase in the Ca^{2+} concentration in the blood due to ↑ of Ca^{2+} reabsorption by the kidneys, ↑ of bone resorption and ↑ of calcitriol production in the kidneys
Heart	Atrial natriuretic peptide (ANP)	Peptide	↓ of Na^{+} reabsorption by the kidneys; ↑ of diuresis
Ovaries	Estrogens (estradiol, estriol, estrone) produced by granulosa cells	Steroids	↑ of reproductive organs development, regulation of menstrual cycle, maintenance of pregnancy, control of secondary sex characteristics; metabolic effects (decrease rate of bone resorption, protect from endothelial dysfunction, increase HDL and decrease LDL concentration in the blood), influence on the immune system
	Progesterone, produced by corpus luteum cells	Steroid	Regulation of menstrual cycle, maintenance of pregnancy, influence on the immune system
	Androgens (androstenedione, testosterone, and in a less amounts –	Steroids	Substrate of aromatase reaction, especially during menopause; regulation of folliculogenesis, control of bone and

	dehydroepiandros-terone) produced by the theca cells, granulosa cells and ovarial stroma		muscular system development, control of voice timbre, ↑ of EPO secretion by the kidneys, metabolic effects, control of sexual behavior, influence on the immune system
Testes	Androgens (testosterone produced by Leydig cells and dihydrotestos-terone)	Steroids	Anabolic effects, ↑ of genitalia growth, development of secondary sex characteristics, spermatogenesis, ↑ of EPO secretion by the kidneys, metabolic effects, control of sexual behavior, influence on the immune system

↑ – Stimulation; ↓ – Inhibition

Effects of insulin and counter-regulatory hormones were discussed in the Textbook "General pathophysiology: the essentials" (Part XI).

According with their chemical structure, hormones are water-soluble proteins (GH, TSH, ACTH, FSH, LH, PRL, insulin, glucagon, anti-Müllerian hormone, leptin), small peptides or amines (epinephrine, norepinephrine, thyroxin, T_3) or water-insoluble steroids (cortisol, aldosterone, testosterone, estradiol). Hormones may be fully active when released in the blood (for, example, GH and insulin) or may require preexisted activation (conversion of testosterone to more active dihydrotestosterone by the enzyme 5α-reductase). Abnormal peripheral conversion of hormones is a cause of some endocrine diseases.

Secretion of hormones undergoes to rhythmic fluctuations – minute, hourly, daily, monthly or seasonally due to specific rhythm of activity of clock genes, which control hormonal secretion. Maximal daily concentration of some hormones is illustrated in the Fig. 7-1. Abnormal circadian rhythms or so-called "circadian dyssynchrony" (following sleeplessness, working at nighttime, etc.) may impair secretion of melatonin, which is a master of circadian rhythms regulation, thus altering cyclic secretion of hypothalamic hormones.

In the bloodstream hormones may be free or bound with proteins (for instance, thyroid hormones bind to thyroxin-binding globulin; sex hormones combine with sex-hormone binding globulins; binding of some hormones with albumins). That is why abnormal synthesis of hormone binding proteins (in patients with liver cirrhosis, severe inflammation) may lead to different endocrine disturbances.

Receptors for hormones may be localized in the cell membrane, cytoplasm and nucleus. There are several classes of hormone receptors. Hence, receptors to parathyroid hormone, TSH, ACTH and LH relate to 7-transmembrane (serpentine-like) domain receptors coupled with guanylate nucleotide binding proteins or G-proteins. Activation of G-proteins results in the activation of adenylate cyclase and phospholipase C. Some receptors (for example, for insulin) associate with tyrosine

kinases regulating via phosphorylation/dephosphorylation and activation of related mitogen activated protein kinases (MAP kinases). Cytokine receptors (for instance, for growth hormone and leptin) link to tyrosine kinases and are regulated via phosphorylation/dephosphorylation with subsequent activation of STATs (Signals Transducers of Activators of Transcription). Other receptors (for low density lipoproteins, transferrin, ANP) are ligand regulated transporters, which undergo to endocytosis to cause their biological effects. Steroid hormones, thyroid hormones, retinoids, vitamin D, fatty acids and prostaglandins have nuclear receptors, which after translocation in the nucleus and binding with DNA mediate activation or repression of transcription ("genomic" action of hormones). However, steroid hormones bind with membrane-associated protein kinases in caveolae – membrane invaginations and activate different kinase cascades thus possessing so-called "non-genomic" fast changes.

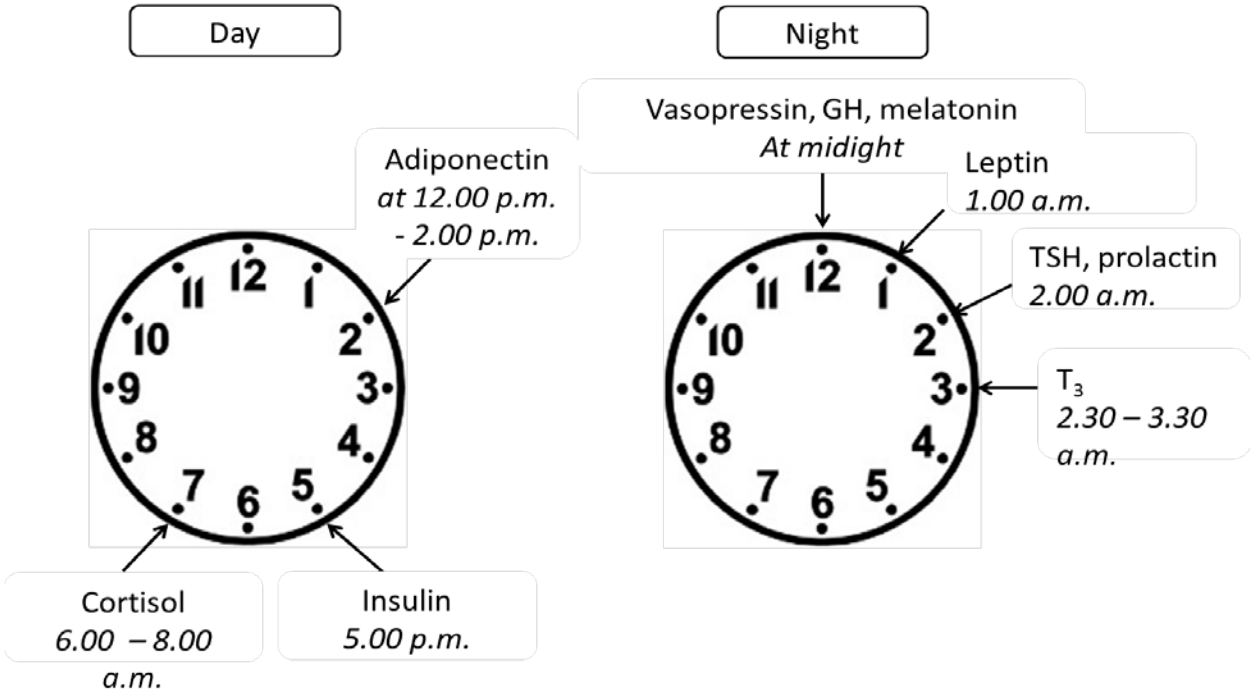


Figure 7-1. Time-of-day dependent oscillations in hormones concentration in the blood

Hormones may act distant (endocrine or intracrine) or local (paracrine or autocrine, Fig. 7-2).

Different feedback mechanisms, both negative and positive, maintain hormonal homeostasis. Hence, according with negative feedback mechanisms, increased concentration of thyroid hormones will suppress secretion of both hypothalamic TSH-releasing hormone and pituitary TSH. In contrast, decreased concentration of T_3 and T_4 will stimulate secretion of TSH-releasing hormone and TSH (Fig. 7-3). Stimulation of FSH and LH surge in the middle of menstrual cycle by high concentration of estrogens and progesterone is an example of positive feedback mechanism. Maintenance of calcium homeostasis and glucose level in the

blood is not within the scope hypothalamic-pituitary feedback regulation.

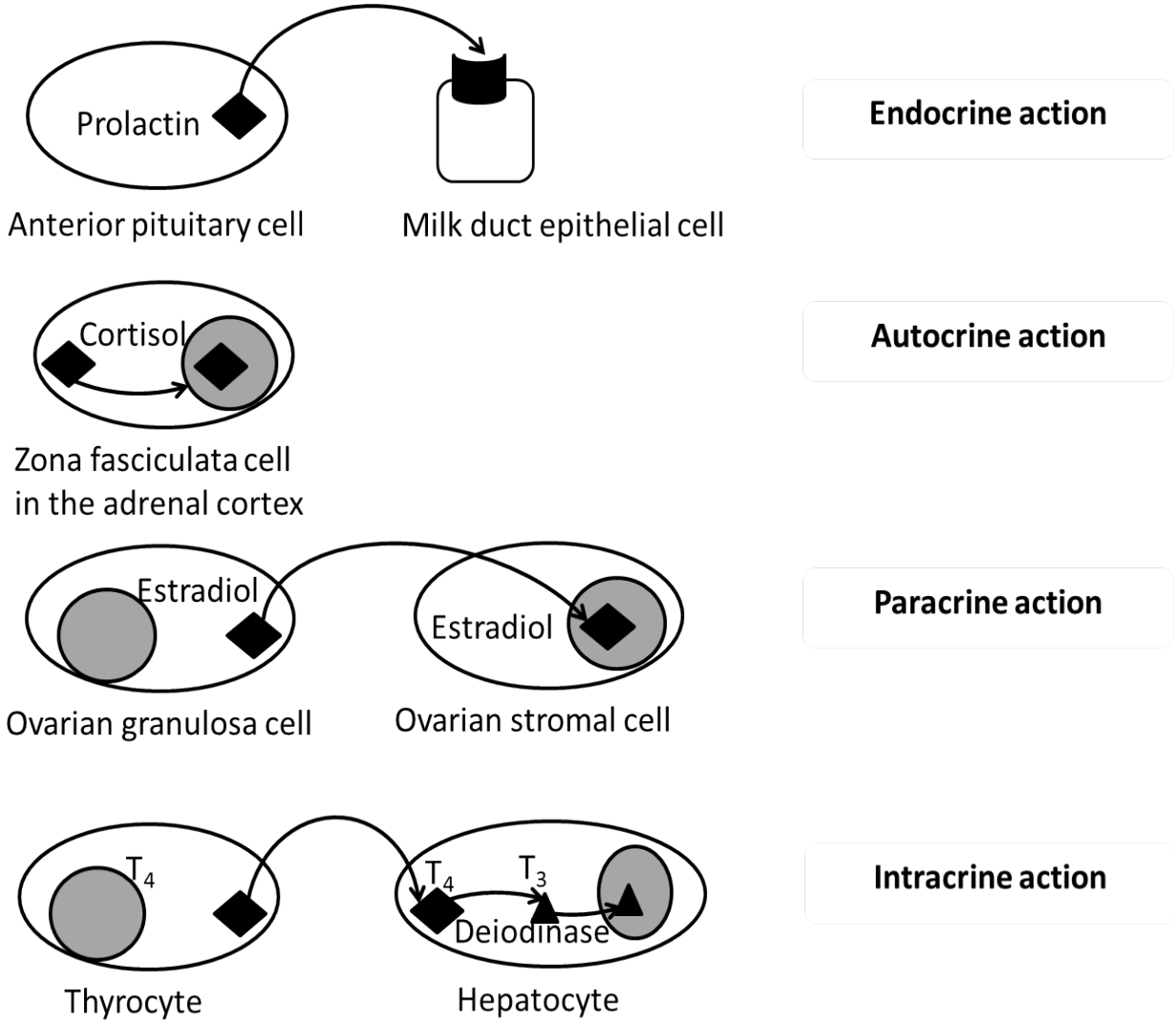


Figure 7-2. Mode of hormone action

T_3, triiodothyronine; T_4, thyroxine

Such knowledge is useful for the detection of primary, secondary and tertiary endocrine disorders:

- Primary endocrine disorders are resulted from damage of so-called "peripheral" endocrine glands (thyroid gland, gonads, and adrenals) and characterized by impaired production of hormones by these glands. According with negative feedback mechanisms, concentrations of corresponding pituitary trophic hormones will be changed. For instance, patients with primary hypothyroidism have decreased T_3 and T_4 concentrations, but elevated TSH level in their blood serum. Primary hypergonadism in males is characterized by excessive testosterone concentration and corresponding reduced LH level in the serum.
- Secondary endocrine disorders are caused by inadequate secretion of hormones from the anterior pituitary gland with unidirectional change in hormone secretion

by corresponding "peripheral" endocrine gland. For example, decreased serum level of T_3, T_4 and TSH indicates primary (or tertiary) hypothyroidism. Elevated serum concentration of ACTH and cortisol indicates secondary hypercorticism.

- Tertiary endocrine disorders are due to abnormal secretion of corresponding statins or hypothalamic releasing hormones from the hypothalamus.

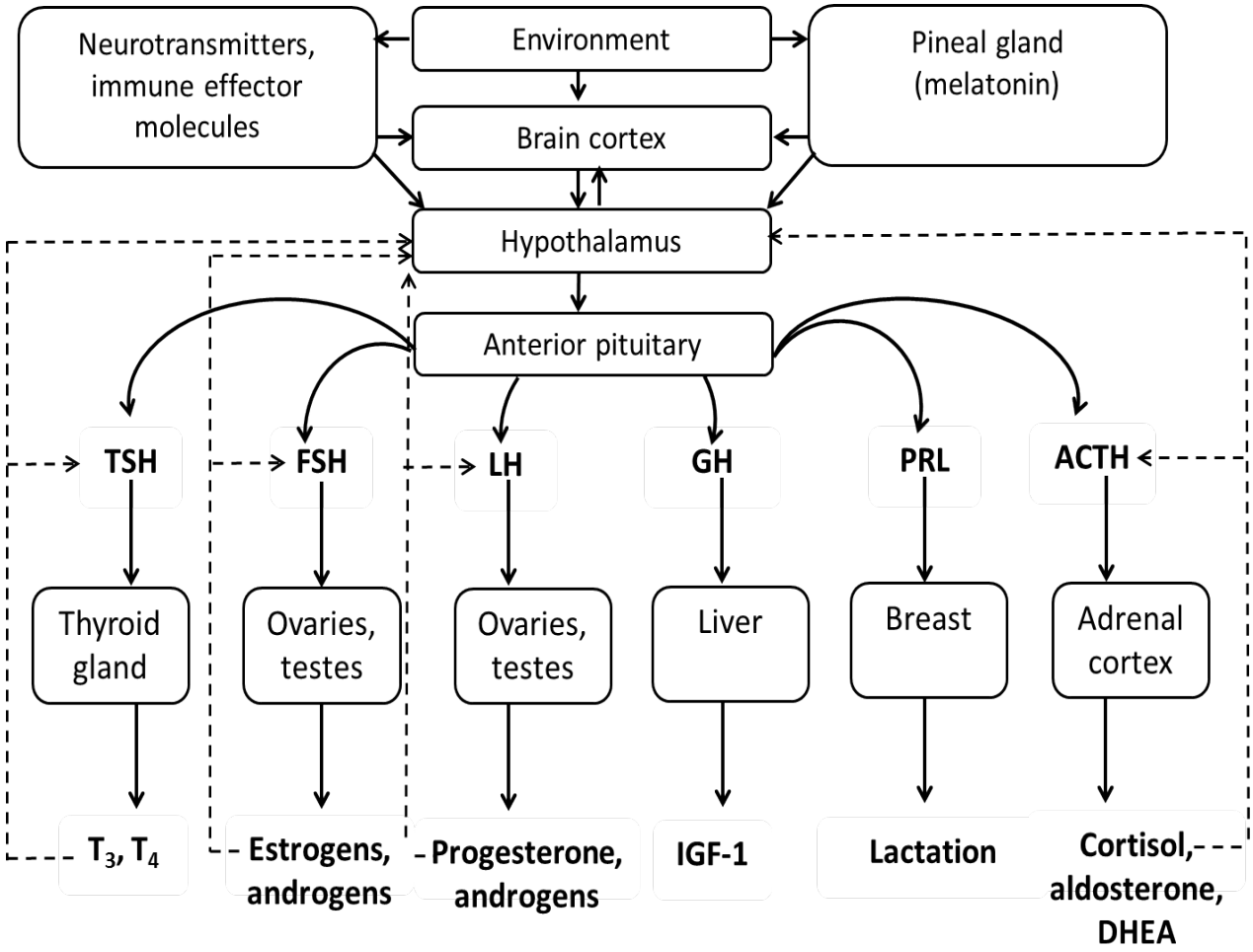


Figure 7-3. Hypothalamic-pituitary-target organs feedback mechanisms
Dashed lines indicate negative feedback

Decreased hormone concentration often up-regulates receptors to the hormone thus resulting in sensitization. In contrast, excessive level of any hormone decreases number of receptors resulting in a decrease in hormone sensitivity. Such adaptation is caused by inducing or repression of the receptor gene transcription. Feedback mechanisms may impair during different disorders. For instance, hormone secreting tumors usually demonstrates unresponsiveness to negative feedback mechanisms. It is important to keep in mind that exogenously introduced hormones as drugs can impair feedback mechanisms. Glucocorticoids, which are widely used as a potent anti-inflammatory drugs, suppress own cortisol and ACTH secretion.

Disorders of hormones inactivation and excretion may lead to different en-

docrine disorders. These mechanisms are proteolysis of peptide hormones, oxidative deamination of catecholamines, hydroxylation of steroid hormones, and conjugation of thyroid hormones with glucuronic acid.

Hormonal disorders can be classified into:

- Congenital or acquired;
- Primary, secondary or tertiary (See above);
- Monoglandular (affecting only one endocrine gland) or polyglandular (affecting several endocrine glands);
- Total (with alteration of all hormones production in the affected endocrine gland) or partial (with alteration of selected hormones secretion by the affected endocrine gland);
- Manifest by decreased or increased hormonal effects.

Basic overview of etiology of hormonal abnormalities is summarized in the Table 7-2.

Table 7-2. General causes and mechanisms of endocrine disorders

Endocrine disorders with decreased hormonal effect	
Basic mechanisms	Clinical examples
1. Decrease in hormone synthesis and/or storage due to:	
Congenital hypo- or aplasia of the endocrine gland	DiGeorge syndrome with hypoplasia of parathyroid glands and corresponding hypocalcemia and primary immunodeficiency due to hypoplasia of the thymus
Damage and necrotic death of hormone-secreting cells after prolonged ischemia, irradiation exposure, trauma, hemorrhage; in infiltrative and autoimmune diseases	Sheehan's syndrome (total or partial hypopituitarism after necrotic death of the pituitary hormone-producing cells after severe postpartum bleeding; Autoimmune-mediated oophoritis; Diabetes mellitus complicated hemochromatosis
Disorders of regulation of hormonal production	Stress-induced hypersecretion of ACTH with impairment of FSH, LH, estrogens and progesterone secretion in "female athletes triad" which is manifested by (1) inadequate nutrition; (2) amenorrhea; (3) osteoporosis due to hypoestrogenemia
Lack of receptors for stimulating hormones	Autosomal recessive growth hormone deficiency due to lack of receptors to the GHRH in the anterior pituitary
2. Synthesis of hormones with less than normal biological activity	Synthesis of insulin with lack of biological activity due to it abnormal structure in some rare familial cases of diabetes mellitus; autosomal-recessive carbohydrate deficiency glycoprotein syndrome

	with abnormal glycosylation of FSH and hypergonadotropic hypogonadism
3. Decrease of binding of hormones with proteins	Estrogen-dependent hyperproduction of the sex hormone binding globulin with subsequent reduction of free and metabolically active sex hormones concentration in the blood
4. Rapid inactivation of hormones	Increased aromatase activity in males with liver cirrhosis, which leads to higher androgens to estrogens conversion rate with clinical signs of hyperestrogenemia (gynecomastia, testicular atrophy, impotence) in affected males
5. Lack of peripheral conversion of the hormone to most active form	5α-reductase deficiency in males with poor peripheral conversion of testosterone to more active dihydrotestosterone. Affected newborn bows with normal karyotype 46, XY have ambiguous external genitalia and lack of virilization at puberty. This male pseudohermaphroditism is characterized by high testosterone/dihydrotestosterone ratio.
6. Unresponsiveness of target organ due to:	
Decrease in receptor number and/or inadequate binding of the hormone with receptor	Androgen insensitivity syndrome, which manifests in affected individuals with 46, XY karyotype by the feminization of external genitalia at birth, abnormal sexual development, primary amenorrhea and infertility (phenotypically patients are females). Complete form of the syndrome is resulted from mutations in the X-linked androgen receptor gene; Autosomal-recessive GH deficiency due to decrease in GHRH receptors number in the anterior pituitary gland
Blockage of receptors	Some forms of diabetes mellitus with insulin resistance due to binding of autoantibodies with insulin receptors; Nephrogenic form of diabetes insipidus in patients received lithium salts for the management of bipolar disorder, caused by binding of lithium salts with receptors to ADH in the renal collecting tubules
Disorders of postreceptor signalling	Pseudohypoparathyroidism (Albright hereditary osteodistrophy) as a result of insensitivity to nor-

	mal concentrations of parathyroid hormone due to cAMP-dependent or independent abnormalities in the postreceptor signalling
Endocrine disorders with increased hormonal effect	
1. Increase in hormone release due to:	
Hyperplasia	Congenital adrenal hyperplasia with hyperandrogenemia
Adenoma	ACTH-secreting pituitary adenoma, prolactin-secreting pituitary adenoma, T_3 and T_4-secreting adenoma of the thyroid gland
Hyperstimulation	Increased production of pituitary tropic hormones with activation of corresponding target endocrine glands
Ectopic hormone production (outside of the endocrine gland)	Releasing of ACTH from the small adenocarcinoma in the lung; secretion of GH by neoplastic cells from the stomach adenocarcinoma; secretion of prolactin by endometrial cancer cells (paraneoplastic syndrome)
2. Decrease in the hormone binding with carrying proteins	Decrease in thyroxine-binding globulin synthesis in the liver as a part of acute phase response during severe inflammation with corresponding elevation of free T_3 and T_4 concentration; decrease in sex hormones binding globulin in obese females with hyperandrogenemia and hyperestrogenemia
3. Hypersensitivity of the target organ to the hormone due to:	
Increase in receptors number	Expression of receptors to hormones in tumor cells
Increase in sensitivity of receptors to the hormone	Dominant activating LH receptor gene mutation which results in receptor coupling with G-proteins and corresponding postreceptor signaling even without LH manifesting by the male-limited precocious puberty
Stimulation of receptors by other than hormone stimuli	Grave's disease (autoimmune thyroiditis, which is caused by binding of thyroid stimulating antibodies with TSH receptors and resultant hyperthyroidism); activation of estrogen receptors by endocrine-disrupting chemicals with estrogen-like activity
4. Delayed inactivation of	Hyperprolactinemia in patients with chronic kid-

hormones	ney disease (chronic renal failure) or liver cirrhosis due to impaired prolactin clearance and excretion

Different endocrine disorders trigger compensatory mechanisms including:

- Changes in storage of the hormone precursors in the endocrine gland;
- Activation of feedback mechanism;
- Reparative regeneration;
- Compensatory hypertrophy or atrophy;
- Changes in hormones binding with plasma proteins;
- Changes in hormones inactivation and elimination rate;
- Changes in sensitivity of target organs to hormones.

Diagnostic approaches in the endocrinology

1. Blood tests. Endocrine function can be accessed by measuring concentration of basal circulating hormones with ELISA method (for example, measuring of T_3, T_4, PRL, and IGF-1 concentrations in the morning serum samples).

2. Suppression or stimulation tests. Stimulation tests are recommended to prove or exclude hypofunction of the endocrine gland. For instance, ACTH-stimulation test reveals stimulated cortisol secretion. Poor cortisol secretion indicated hypofunction of adrenals. Metoclopramide stimulating test evaluates stimulated prolactin secretion. Inadequate augmentation in prolactin concentration indicates inability of the pituitary lactotrophs to produce prolactin. Poor response of anterior pituitary to TRH and low level of TSH after such stimulation reflects hypofunction of the anterior pituitary. Suppression tests are used when hyperfunction of any thyroid gland or ectopic hormone production are suspected. Thus, glucose load normally suppress GH secretion. Lack of such response indicated probable GH-secreting pituitary adenoma. Dexamethasone suppression test is used to assess suppressed cortisol production. Inadequately high cortisol concentration after such test helps to suspect cortisol or ACTH-producing tumor.

3. Measurement of hormone-binding proteins and antibodies to hormones.

4. Measurement of hormone metabolites in the blood and/or urine. For example, catecholamine-secreting tumors may be suspected after detection of high concentration of vanillylmandelic acid in 24h-urinary tests.

5. Measurements of substances, whose concentration is a result of hormonal regulation (for instance, detection of glucose, ketone bodies, electrolytes, proteins, etc. in the blood).

6. Urine tests are used in case of daily hormone fluctuations (for example, concentration of 17-ketosteroids is measured in the 24 h-urinary samples).

7. Genetic testing to reveal backgrounds of the underlying endocrine disorder.

8. Imaging methods (magnetic resonance imaging, MRI; computer tomogra-

phy scanning, CT; ultrasonographic scanning; positron emission tomography, PET for detection of endocrine neoplasms).

9. Biopsy (for instance, fine-needle aspiration of the thyroid gland).

Disorders of the hypothalamus

These disorders can be classified into congenital and acquired; caused by morphological abnormalities (due to congenital embryopathies, tumors, inflammatory diseases, hydrocephalus with increased intracranial pressure, infiltrative diseases, vascular diseases, irradiation exposure and nutritional disorders, for instance, Wernicke's disease) or by functional changes (resulted from psychosocial deprivation, excessive weight loss or extreme exercises). Disorders of the hypothalamus might manifest at any age – immediately after birth, during childhood, in adults or in aging individuals. Hypothalamic disorders are resulted from the partial or total increased or decreased secretion of hypothalamic hormones (See table 7-1) and manifests by the clinical and laboratory signs of pituitary hyperfunction or pituitary hypofunction, accordingly. Pituitary hypofunction due to hypothalamic disorders may lead to growth hormone deficiency, hypothalamic hypogonadism, hypothalamic hypothyroidism, hypothalamic ACTH deficiency and diabetes insipidus. Pituitary hyperfunction caused by hypothalamic disorders usually manifests by hypothalamic hypergonadism, hypothalamic hyperprolactinemia, hypothalamic acromegaly or gigantism (these pathologies will be discussed later). However, because of the hypothalamus is a "crossroad" in the neuroendocrine and immune axis, neuropsychiatric symptoms, behavioral abnormalities, autonomic and metabolic disorders are relatively common in patients with hypothalamic diseases. Such patients may have disorders of thermoregulation varying from hypothermia or hyperthermia to poikilothermia, impaired sweating, sphincter disorders, cardiac arrhythmias, disorders of nutritional behavior (anorexia nervosa or bulimia), compulsive water drinking or adipsia, disorders of sleep and consciousness, hallucinations, epilepsy and hypersexuality. Let us discuss some congenital hypothalamic disorders.

Kallman syndrome is a result of gene KAL1 or gene encoding 1st type of receptor to the fibroblast growth factor mutations with X-linked, autosomal dominant or autosomal recessive type of inheritance. Such mutations result in abnormal synthesis of anosmin, protein of the extracellular matrix, and in olfactory bulbs agenesis or hypoplasia. Affected individuals have abnormal GnRH secretion with hypogonadotropic hypogonadism (with low FSH and LH concentration) and anosmia. Affected girls suffering from the primary amenorrhea and infertility at adulthood; affected boys demonstrate delayed puberty, and have less pronounced secondary sex characteristics compared with normal individuals.

Prader-Willi syndrome is caused by gene mutations in the chromosome 15q. Affected patients have abnormally low GnRH secretion with hypogonadotropic hypogonadism in both sexes, abnormal physical development during puberty, muscular hypotonia, different dysmorphic features, glucose intolerance, arterial

hypotension and mental retardation.

Laurence-Moon-Biedl syndrome is characterized by an abnormal GnRH secretion, hypogonadotropic hypogonadism, polydactilia, obesity, mental retardation and retinitis pigmentosa with blindness at age 30. Sometimes affected patients may have central diabetes insipidus due to ADH hyposecretion.

Anterior pituitary disorders

Hypopituitarism, or decreased secretion of pituitary hormones, may be partial (with diminished production of one of several pituitary hormones) or total, with decreased secretion of all pituitary hormones (See Table 7-1). Hypopituitarism may be resulted from the loss of hypothalamic stimulation or direct loss of the pituitary hormones. If hypopituitarism is accompanied by diabetes insipidus or hyperprolactinemia, one should keep in mind hypothalamic causes of hypopituitarism.

Hypopituitarism can be classified into congenital or acquired. Congenital disorders are inherited an autosomal dominant or autosomal recessive manner. Gene mutations may be detected at any level of pituitary hormones secretion: mutations affecting genes encoding receptors for the hypothalamic releasing hormones, mutations affecting structural genes for pituitary hormones, and mutations affecting organ receptors to pituitary hormones.

Most common causes of hypopituitarism are pituitary adenomas. Pathogenesis of hypopituitarism complicated pituitary adenomas is following: (1) adenoma causes compression or destruction of the normal pituitary cells; (2) impairment of pituitary blood supply; (3) hemorrhage into adenoma leads to pituitary infarction. Other causes of hypopituitarism are radiation, persistent rise of intracranial pressure, pituitary apoplexy, pituitary infarction, infiltrative diseases, iron deposition during hemochromatosis, systemic amyloidosis and some functional causes which are identical to those discussed above in hypothalamic disorders. Selected forms of hypopituitarism are discussed below.

Sheehan's syndrome is an infrequent cause of hypopituitarism which is resulted from pituitary acute necrosis due to severe postpartum hemorrhage. Physiological pituitary enlargement during pregnancy gives it susceptible to blood flow reduction following severe acute hemorrhage. Favorable conditions for this syndrome include preeclampsia with microcirculatory disorders and use of uterotonic drugs for myometrium contractility stimulation. Acute necrosis most commonly affects corticotrophs with ACTH deficiency and thyrotrophs with corresponding TSH deficiency producing partial hypopituitarism and hypofunction of the adrenal cortex and thyroid gland, accordingly. However, in some severe cases hypopituitarism may be total, with reduced secretion of all anterior pituitary hormones and even MSH. In postpartum period such panhypopituitarism manifests by failure of lactation, clinical signs of hypothyroidism, adrenal cortex insufficiency with loss of pubic and axillary hair (due to loss of androgens of adrenal cortex origin), paleness (due to MSH deficiency), metabolic disorders and amenorrhea in future.

Hyperpituitarism, or increase in pituitary hormones synthesis and secretion, may be partial and total, congenital or acquired. Excessive concentrations of pituitary hormones stimulate corresponding endocrine glands with clinical and laboratory signs of their hyperfunction. Hyperpituitarism results from different pathologies, including hypothalamic disorders with abnormally high production of releasing factors and/or low secretion of factors inhibiting pituitary hormones secretion, adenoma or hyperplasia of the pituitary gland, carcinoma, which is originated from the pituitary cells or secretion of hypothalamic hormones by extrapituitary tumors (paraneoplastic syndrome). Most common cause of hyperpituitarism is a pituitary adenoma. According with their size, adenomas can be classified into microadenomas (with diameter less than 1 cm) or macroadenomas (having diameter more than 1 cm). Adenomas usually secrete some pituitary hormones and produce local effects, especially if they compress surrounding cranial structures after adenoma extends sella turcica, for instance, compression of the optic chiasm results in visual abnormalities. Some adenoma-related syndromes (headache, nausea, vomiting) relate to increased intracranial pressure. Acute hemorrhage in adenoma results in pituitary apoplexy with subsequent acute nerve palsy, severe headache and hypopituitarism.

Disorders of growth hormone production

Normally synthesis and secretion of GH is under the control of different factors. Among these stimulators are following:

- Hypothalamic GHRH, ghrelin, prolactin, sex steroids, stress, deep sleep, physical exercises, activation of the α-adrenoreceptors in the pituitary gland, acetylcholine, fasting, amino acids, hypoglycemia.
- Different factors inhibit GH secretion:
- Somatostatin, **I**nsulin-like **G**rowth **F**actor-1 (IGF-1), glucocorticoids, obesity, increased free fatty acids concentration, activation of the β-adrenoreceptors in the pituitary gland, hyperglycemia, hypothyroidism, emotional deprivation.
- Maximal concentrations of GH are detected in the blood during puberty. In the blood GH binds with at least six different binding proteins, which dampen daily fluctuations of GH concentration in the blood. Growth and metabolic effects of GH are mediated by itself or by IGF-1 (somatomedin C). GH stimulates IGF-1 production in most tissues, where IGF-1 mediates growth-promoting, anabolic and mitogenic effects of GH. Besides the stimulation of linear growth, GH is responsible for some metabolic effects. It induces lipolysis and stimulates amino acids uptake and synthesis of proteins thus causing positive nitrogen balance. GH is thought to be an insulin-counter regulatory hormone. Main site of GH destruction is kidneys.

Causes of **growth hormone deficiency** are following:

- Mutations of genes encoding GHRH receptor, GH, GH receptor, IGF-1 receptor;
- Diseases affecting hypothalamus and anterior pituitary (See above);
- Psychosocial deprivation;
- Endocrine and somatic diseases affecting GH secretion and clearance.

The clinical manifestations of GH deficiency depend on the time of disease onset. Affected children have slow linear growth rate, usually less than 3 cm/year. Body proportions are normal. Affected individuals have increased fat mass, decreased muscle mass, and smaller hearts with lower cardiac output. Higher serum lipids concentration, abdominal adiposity and insulin resistance are risk factors for atherogenesis. Patients may have hypoglycaemia due to corresponding cortisol deficiency. Besides these symptoms, affected individuals suffer from decreased physical activity, emotional lability, social isolation, and disturbances in sexual functions. Low level of GH and/or normal or decreased IGF-1 concentrations may be detected in patients' blood. However, insulin tolerance test is the "gold standard test" for GH deficiency evaluation. Insulin-induced hypoglycemia must stimulate GH release. Individuals with GH deficiency have blunted response to insulin.

Pathophysiological basis for the treatment of GH deficiency: (1) management of the underlying disorder if possible; (2) in children to increase final height recombinant GH as injections is recommended.

Growth hormone excess is resulted from different causes:

- Hypothalamic GHRH hyperproduction in hypothalamic tumors;
- Peripheral GHRH hyperproduction by neoplastic cells of some tumors as an example of a paraneoplastic syndrome (bronchial carcinoid, pancreatic islet-cell tumor, small-cell lung cancer, adrenal adenoma, medullary thyroid carcinoma, pheochromocytoma);
- Pituitary GH hyperproduction in pituitary adenoma or pituitary carcinoma;
- Extrapituitary GH-secreting tumors (pancreatic islet-cell tumor, lymphoma);
- Iatrogenic GH excess as a result of GH overdosing following management of GH deficiency;
- Some rare familial syndromes (multiendocrine neoplasia syndrome type 1, McCune-Albright syndrome, familial acromegaly, Carney's syndrome).

GH excess starting before puberty and the closure of the epiphyses of the long cortical bones leads to gigantism (tall stature, Fig. 7-4), whereas GH overproduction after puberty results in acromegaly manifesting by increased growth of the ends of extremities. Most effects are related to GH-induced elevation of IGF-1 concentrations in different organs and tissues. Symptoms of GH excess after puberty are illustrated in the Fig. 7-5. It is important to note, that excessive GH concentrations impair pulsatile secretion of gonadotropins and prolactin with corresponding endocrine disturbances. Pathogenesis of arterial hypertension in patients with GH excess was discussed earlier in the Part of the present Textbook "Disorders of regula-

tion of vascular tone. Arterial hypertension. Arterial hypotension."

Figure 7-4.
Fedor Machnov (1878-1912), a peasant of Vitebsk province
F.A. Machnov was the tallest individual on the Earth. His height was 285 cm, foot and palm length was 51 and 31 cm, accordingly. He died from undifferentiated lung disease, perhaps, tuberculosis.

The diagnosis of GH excess is confirmed after revealing the fact that oral glucose administration is unable to suppress GH production, because of GH secretion is pulsatile and random GH elevation is not useful for diagnosis of GH excess.

Pathophysiological basis for the treatment of GH-secreting adenoma:

(1) Transsphenoidal surgical removal of adenoma;

(2) Radiotherapy;

(3) Somatostatin analogues (octreotide);

(4) GH receptor antagonists (pegvisomant);

(5) Dopamine agonists (bromocriptine, cabergoline) to suppress GH and prolactin hypersecretion.

Disorders of prolactin production

Prolactin (PRL) is produced in most concentrations by the pituitary lactotropes, which originate with somatotropes, from the common precursor. That is why adenomas often secrete GH and prolactin together. Other sources of prolactin are epithelial cells of mammary glands, endometrial cells, cells of placenta, and T-cells. The major PRL function is stimulation of milk secretion by epithelial cells in breast ducts, however at least 300 other functions of PRL were described in mammals. In female reproductive system PRL is responsible for development of corpus luteum and maternal behavioral control after delivery. PRL also suppresses libido in both sexes. Secreting lactotropes normally are under the inhibiting control of

dopamine, so decrease in dopamine secretion may lead to hyperprolactinemia. Other hypothalamic, local and systemic factors regulate prolactin secretion.

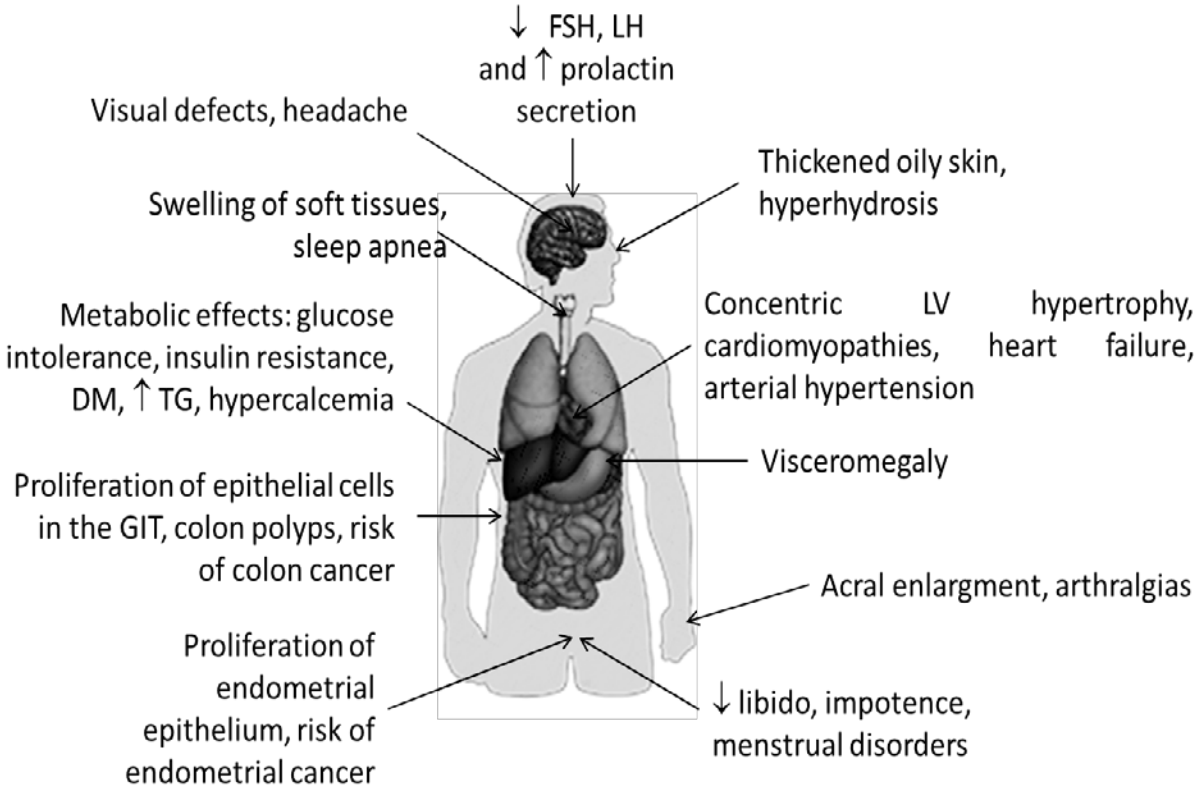


Figure 7-5. Clinical symptoms of acromegaly

Stimulators of PRL secretion are: estrogens, opioid peptides, cholecystokinin, serotonin, vasointestinal peptide, TRH and suckling.

Most important inhibitor of PRL secretion is dopamine, however, bombesin, neurotensin, GABA, endothelins, NO, thyroid hormones and glucocorticoids inhibit PRL secretion too.

Hypoprolactinemia as an isolated deficiency of pituitary hormones is rare and occurs primarily with other hormones deficiency. The only documented effect of PRL deficiency is the absence of lactation after delivery. Breast development is normal in females with PRL deficiency. Level of the PRL in the blood is low, and TRH stimulation test reveals no any rise of PRL concentration.

Hyperprolactinemia may be physiological (during pregnancy and lactation) and pathological. Causes of pathological hyperprolactinemia may be functional or related to different underlying disorders. Functional causes of PRL excess are following:

1. Disorders of hormonal state – hyperestrogenemia, hyperandrogenemia. Estrogens and androgens, after their conversion to estrogens by aromatase, suppress activity of dopaminergic neurons thus leading to hyperprolactinemia.
2. Repeated stress, surgery, electric trauma, vigorous physical exercises, and repeated hypoglycemic episodes after insulin overdosing lead to functional disor-

ders of the hypothalamic-pituitary system thus elevating PRL level in the blood.

3. Use of some drugs:
   - Neuroleptics, especially of the first generation, which impair neuronal dopamine transport;
   - Serotonin receptors agonists, serotonin reuptake inhibitors, and monoaminooxidase inhibitors which impair activity of the hypothalamic dopaminergic system;
   - Morphine, matadone and metenkephaline analogs, which suppress dopamine secretion in the middle elevation;
   - Antagonist of dopamine receptors (type 2), which are used in the gastroenterology – prokinetics metoclopramide and domperidon, and H_2-histamine receptor blockers (cimetidine, ranitidine) stimulate PRL secretion;
   - Calcium channel antagonist verapamil, dopamine synthesis inhibitor α-methyldopa, catecholamine depletory reserpine via suppression of dopamine release lead to hyperprolactinemia;
   - Oral contraceptives containing estrogens, and antiandrogens stimulate PRL secretion.
4. Transient reflectory hyperprolactinemia (after vein puncture, nipple stimulation, sexual contacts, and after meal rich in amino acids phenylalanine and tyrosine, which impair dopamine secretion).

Hyperprolactinemia may be resulted from different morphological abnormalities in different organs and tissues:

1. PRL-secreting pituitary adenomas are most common causes of hyperprolactinemia. Their incidence during autopsy varies from 15 to 20%, and commonly these macroadenomas were clinically unsuspected.
2. Other hormonally active tumors affecting hypothalamic-pituitary zone. During these tumors synthesis, secretion and dopamine reuptake may be inhibited.
3. Endometrial, intestine, renal, and lung tumors may secrete PRL as a hallmark of the paraneoplastic syndrome.
4. Diseases affecting thyroid gland with its functional insufficiency. According with feedback mechanism, TRH is stimulated, and TRH enchances PRL secretion by lactotropes.
5. Liver and renal diseases with their functional insufficiency lead to hyperprolactinemia due to abnormal metabolism and clearance of PRL.
6. Polycystic ovary syndrome and defects of steroidogenesis in the adrenals, which associate with hyperestrogenemia and hyperandrogenemia and related PRL hypersecretion.
7. Repeated dilation and curettage of the uterus, chest wall trauma, herpes zoster affecting chest wall causes hyperprolactinemia reflectory.
8. Some autoimmune diseases may lead to hyperprolactinemia.

Female patients with hyperprolactinemia suffer from menstrual cycle disorders, infertility and galactorrhea. High PRL concentrations impair pulsatile secretion of GnRH, FSH and LH (Fig. 7-6). Low FSH level in the blood impairs follicu-

logenesis and steroidogenesis in follicles. Prolactin itself binds with receptors to FSH and LH in ovarian cells thus antagonizing of these hormonal effects. As a result, hypoestrogenemia, anovulation, hypomenstrual syndrome, amenorrhea and infertility (or subfertility) are seen. Inadequate gonadotropins concentration also results in gonadal hypoandrogenemia and loss of libido. However, PRL stimulates adrenal androgenic steroids. Poor LH concentrations associate with luteal phase insufficiency and poor pregnancy outcomes due to high risk of miscarriages. Galactorrhea (secretion of milk from non-lactating breast) is detected in up to 80% of affected females.

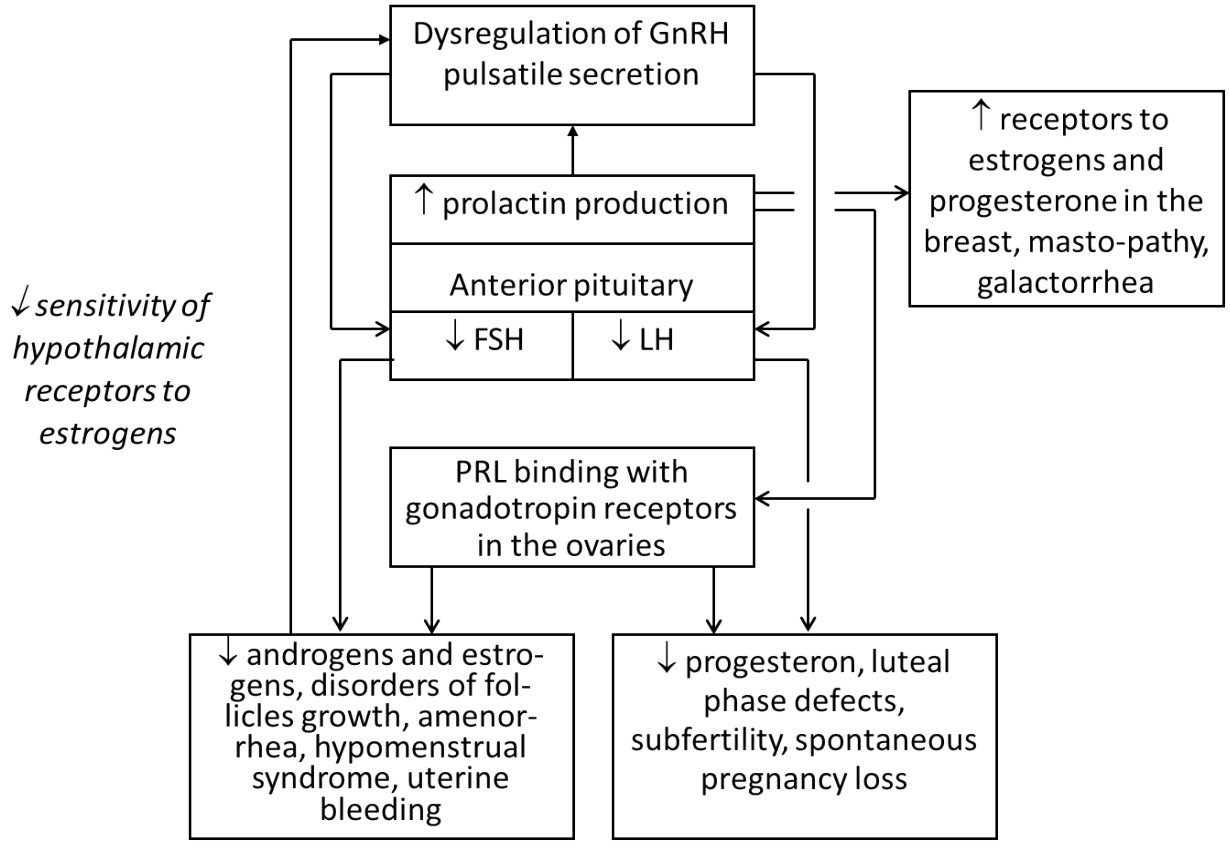


Figure 7-6. Clinical symptoms of hyperprolactinemia in females

Pathophysiological basis for the treatment of hyperprolactinemia: (1) use of dopaminergic receptors type 2 agonists (bromocriptine, cabergoline, pergolid); (2) transsphenoidal resection of macroadenomas; (3) radiotherapy.

Disorders of ACTH production

Adrenocorticotropic hormone is synthetized by adrenocorticotrops in the anterior pituitary from its precursor, pro-opiomelanocortin (POMC) and released in the blood stream by pulsatile manner. POMC also is a precursor of the β-endorphin, β-lipotropin, melanocyte-stimulating hormone (MSH) and some other peptides. The secretion of ACTH is controlled by the hypothalamic-pituitary-adrenal axis. The most important stimulator of ACTH secretion is hypothalamic CRH, which during constant hyperproduction also results in hyperplasia of adre-

nocorticotrops. Other stimulators of ACTH secretion are arginine vasopressin (AVP), locally produced angiotensin II, VIP, catecholamines, gastrin-releasing peptide, some cytokines (TNF-α, IL-1, IL-6, IL-2, and leukemia inhibiting factor), hypoglycemia and physical exercises. In contrast, cortisol is a main inhibitor of both CRH and ACTH secretion. The main effect of ACTH is stimulation of adrenal cortex to produce cortisol, in less extent – aldosterone and adrenal androgens.

ACTH deficiency (secondary hypocortisolism) as an inherited form, coexisting with deficiency of other pituitary hormones and is rare as an isolated form. Injury of the anterior pituitary causes deficiency of several hormones, including ACTH. The most common cause of isolated ACTH deficiency is treatment with exogenous glucocorticoids, which according with negative feedback mechanism suppress both CRH and ACTH secretion with resultant decline in own cortisol production. Isolated ACTH deficiency also may be detected in patient after rejection of pituitary adenoma.

To prove ACTH deficiency and to distinguish primary hypocortisolism from the secondary hypocortisolism stimulating tests are recommended. For instance, insulin-induced hypoglycemia must stimulate ACTH and cortisol production. Affected individuals with damage of hypothalamic-pituitary region usually have blunted response to hypoglycemia. Another test with metyrapone is also useful. Metyrapone inhibits 11β-hydroxylase, which normally converts 11-deoxycortisol to cortisol. Metyrapone-induce decline in cortisol concentration according with feedback regulation mechanism must stimulate ACTH production, but in secondary hypocortisolism such response is significantly attenuated.

Clinically, ACTH deficiency manifests by the signs of hypocortisolism: nausea, vomiting, fatigue, arterial hypotension. Other infrequent symptoms include eosinophilia, hypoglycemia, hyponatremia and loss of libido due to lack of adrenal steroids. Deficiency of ACTH is treated by glucocorticoid replacement therapy.

ACTH excess in most cases is resulted from pituitary ACTH-secreting adenoma (**Cushing's disease**). Other causes of ACTH excess involve ectopic ACTH secretion by extrapituitary tumors (small cell lung carcinoma, thymic carcinoid, islet cell tumors, bronchial carcinoma, pheochromocytoma and some other tumors). In these patients ACTH stimulates adrenal glands to produce mainly cortisol, and to a less extent – aldosterone and androgens. Clinical symptoms of ACTH excess are similar to those observed in primary hypercortisolism (Table 7-3).

Table 7-3. Clinical symptoms of Cushing's disease

Symptoms	Mechanisms of their development
Obesity, hyperglycemia, glucose intolerance	(1) Stimulation of gluconeogenesis and lipogenesis, but lipolysis in the extremities; (2) Glucocorticoids activate hunger center in the hypothalamus; (3) Hyperleptinemia and leptin resistance

Striae	(1) Suppression of connective tissue components synthesis by glucocorticoids; (2) Stimulation of skin distension by adipose tissue
Osteoporosis, high risk of bone fractures	(1) Inhibition of osteoblasts activity and activation of osteoclasts; (2) Stimulation of parathormone synthesis and action; (3) Inhibition of $1,25(OH)D_3$ action on the bone
Arterial hypertension	(1) Stimulation of Na^+ reabsorption by mineralocorticoids and glucocorticoids; (2) Stimulation of angiotensinogen synthesis in the liver and Ang II formation; (3) Increase in endothelin production and decrease in NO synthesis in the vascular endothelial cells; (4) Enhancing in sensitivity of vSMCs to catecholamines
Gastritis, erosions, gastric or duodenal ulcers	Stimulation of gastric juice secretion by glucocorticoids; suppression of protective prostaglandins synthesis in the gastric mucosa
Secondary immunodeficiency	(1) Inhibition of phospholipase A_2 activity by glucocorticoids; (2) Decrease in proinflammatory cytokines formation; (3) Inhibition of antibodies production and suppression of chemotaxis; (4) Suppression of cellular immunity
Virilization in affected females	ACTH-mediated adrenal androgens excessive formation
Reproductive disorders (subfertility, decreased libido, disorders of menstrual cycle)	(1) Disorders of pulsate secretion of GnRH, LH and FSH; (2) Hyperandrogenemia; (3) anovulation

Pathophysiological basis for the treatment of Cushing's disease: (1) selective transsphenoidal resection of the adenoma; (2) pituitary irradiation; (3) "medical" adrenalectomy with drugs suppressing steroidogenesis in the adrenal glands – antimycotic agent ketoconazole, metyrapone, mitonate and some other medications.

Posterior pituitary disorders

Posterior pituitary gland, or neurohypophysis, is the site of antidiuretic hormone (ADH, or arginine vasopressin) and oxytocin secretion; however, these hormones are produced as prohormones in the hypothalamus. The main effect of ADH is reduction of water excretion due to binding with V2 receptors in the kidneys and stimulation of aquaporins-2 or water channels insertion into epithelial cells of the distal tubules and medullary collecting ducts in the kidneys. At highest concentrations ADH is able to produce constriction of vascular smooth muscle cells and smooth muscle cells in the gastrointestinal tract via activation of V1 receptors. Se-

cretion of ADH is controlled mainly by osmoreceptors and transmural pressure receptors in the large blood vessels too. Approximately 10-15% loss of the blood is necessary to stimulate ADH release. The osmostat is located near the third ventricle. It controls ADH release and thirst response. Inability of ADH to regulate fluid retention over than threshold is compensated by the thirst response, because the thirst osmostat has set point approximately 5% higher than ADH osmostat. Other stimuli for ADH secretion are nausea, hypoglycemia, and lack of glucocorticoids, excessive concentration of angiotensin II and smoking.

ADH deficiency can be classified into inherited and acquired. It is manifested by **diabetes insipidus**, which is characterized by polyuria (excretion of a large volume of hypotonic urine) and polydipsia. According with basic pathogenetic mechanism, diabetes insipidus can be classified into:

- Central (hypothalamic) diabetes insipidus;
- Nephrogenic diabetes insipidus;
- Transient diabetes insipidus of pregnancy.

Central diabetes insipidus is resulted from head trauma, transcranial surgery, inflammation, radiation-induced injury, tumors, and infiltrative diseases affecting the hypothalamus and/or posterior pituitary gland, intoxications (caused by snake venom or tetrodotoxin), vascular diseases and congenital malformations. Rare inherited forms of diabetes insipidus with autosomal dominant, autosomal recessive or X-linked recessive trait of inheritance were described. In these cases poor synthesis of ADH prohormone or it secretion from the neurohypophysis were documented. In patients with nephrogenic diabetes insipidus serum ADH concentration is normal, but abnormal V2 receptors count in the kidneys, or impairment of postreceptor signalling, or inadequate aquaporin-2 synthesis and trafficking lead to diminished effects of ADH. Rare X-linked recessive, autosomal recessive or autosomal dominant nephrogenic diabetes insipidus caused by V2 receptors or aquaporin-2 gene mutations were described. Some drugs and chemical substances (demeclocyclin, amphotericin B, aminoglycosides, lithium salts, fluoride, cisplatin) also may lead to nephrogenic diabetes insipidus. This pathology develops also in patients with obstructive nephropathies, ischemic tubular necrosis, amyloidosis and some metabolic disorders such as hypercalcemia, hypercalciuria and hypokalemia. Transient diabetes insipidus of pregnancy is a relatively rare disorder affecting females with normal ADH secretion and response before pregnancy. In certain situations, placenta produces more cystine aminopeptidases – enzymes, which destroy ADH. Patients may return to the normal state after pregnancy.

It is important to note, that secondary ADH deficiency may develop as a result of inadequate ADH response to excessive intake of fluids. Such secondary ADH deficiency is related to several mechanisms: (1) impairment of the “osmostat” activity and “dipsogenic” ADH deficiency; (2) psychogenic polydipsia as a symptom of psychosis; (3) iatrogenic polydipsia, which is based on the recommendation to increase fluid intake. Pathogenesis of the diabetes insipidus is illustrated

in the Fig. 7-7.

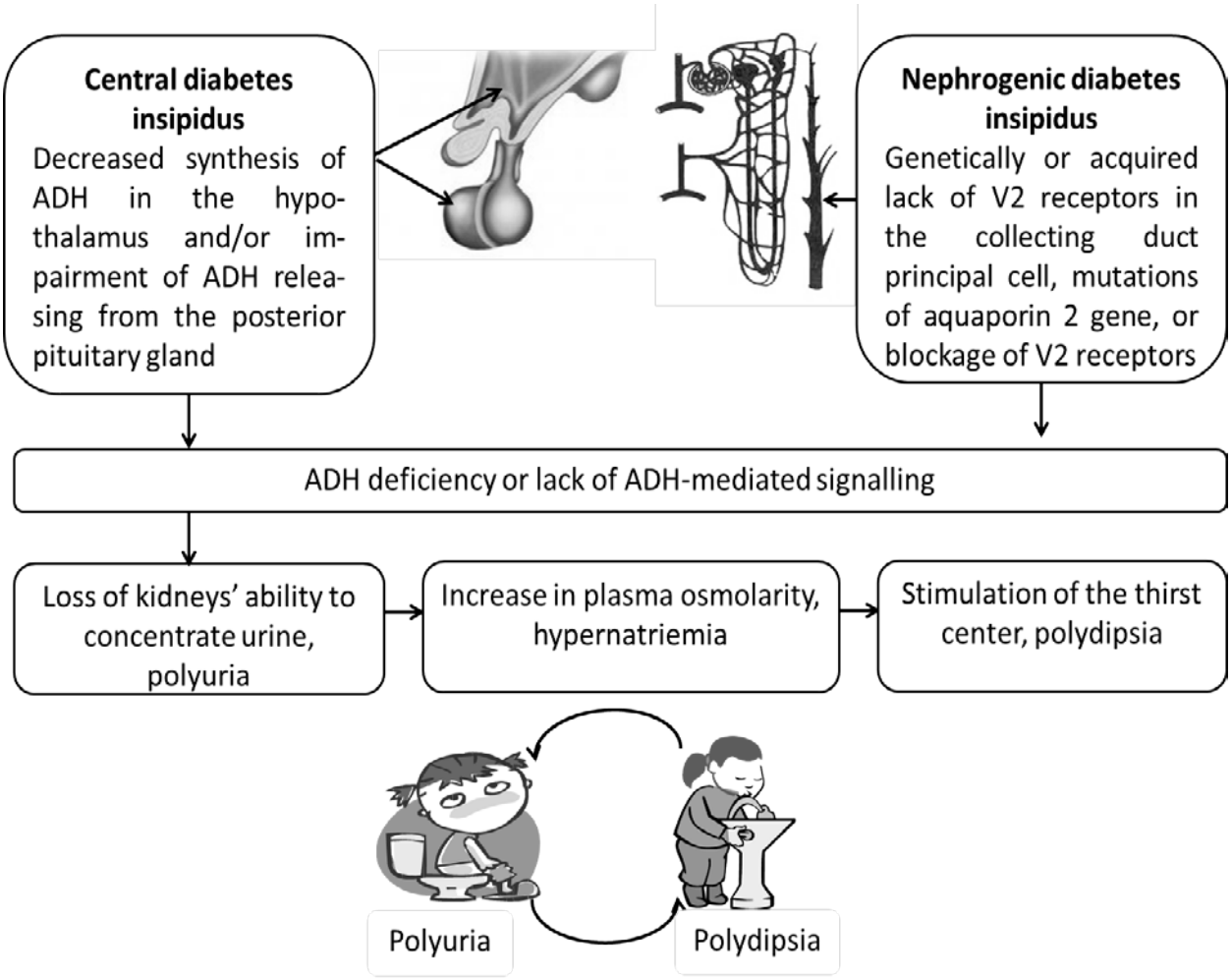


Figure 7-7. Pathogenesis of diabetes insipidus

Reduction of ADH secretion below 80% of normal or blocking of ADH action impairs kidneys' ability to concentrate urine. As a result, polyuria occurs with subsequent increase in plasma osmolarity and activation of thirst response with compensatory stimulation of water intake. Inadequate thirst response or inability to intake adequate amount of fluid for any reason can lead to severe dehydration, and hypertonic encephalopathy with brain shrinkage, coma and seizures.

To distinguish hypothalamic diabetes insipidus from nephrogenic diabetes insipidus ADH injection is recommended. In patients with hypothalamic diabetes insipidus ADH injection must decrease diuresis; no any reduction of polyuria will indicate nephrogenic diabetes insipidus.

Pathophysiological basis for the treatment of diabetes insipidus: (1) to decrease thirst and to maintain normal life style water and water-retaining drugs (L-arginine vasopressin or synthetic analog desmopressin) are recommended for management of hypothalamic diabetes insipidus; (2) thiazide diuretics and/or amiloride, dietary sodium restriction and indomethacin are useful for the treatment of nephrogenic diabetes insipidus.

ADH excess manifests by **syndrome of inappropriate antidiuresis (SIAD).** Causes of ADH excess are following: secretion of ADH by neoplasms as a part of paraneoplastic syndrome (lung carcinoma, pancreatic carcinoma, carcinoids, Ewing sarcoma, mesothelioma, etc.); disorders of osmoregulatory response after head trauma, neuroinfections, vascular diseases, different neurologic diseases, congenital malformations, pulmonary diseases with prominent hypoxia, or drug-induced (caused by vasopressin or desmopressin, oxytocin, nicotine, monoamine oxidase inhibitors, tricyclic antidepressants and some other drugs). Excessive ADH secretion leads to intravascular fluid retention and expansion with hyponatremia (Fig. 7-8).

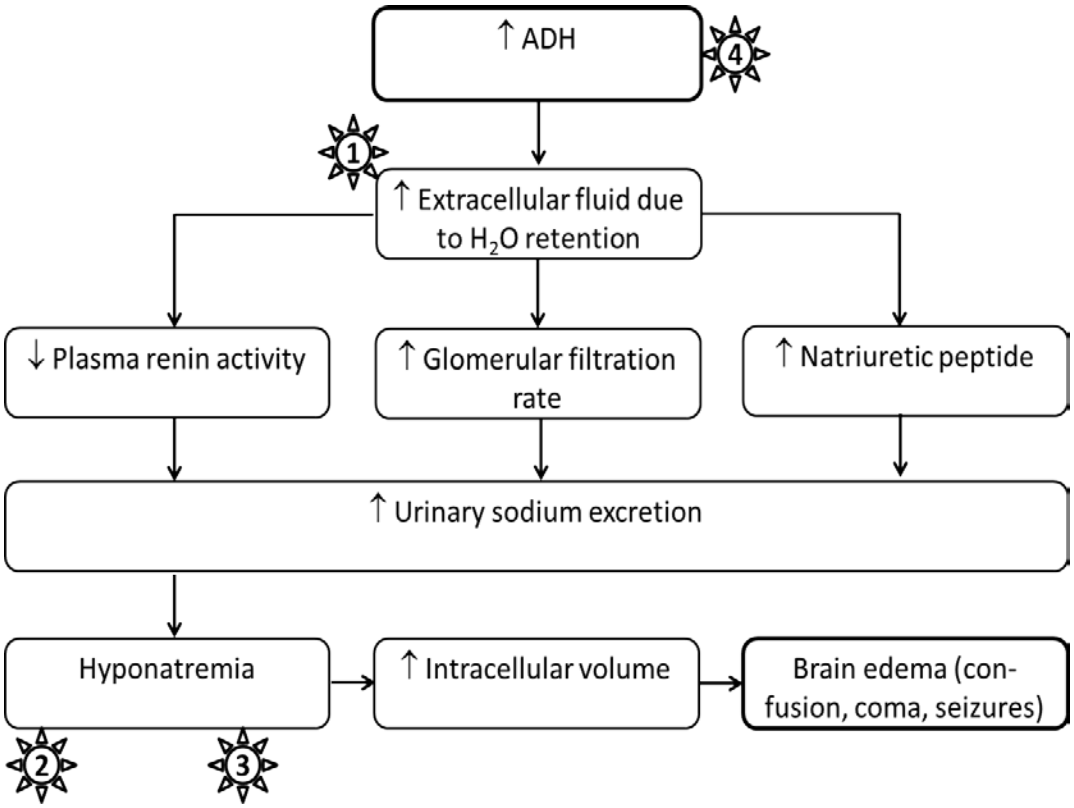


Figure 7-8. Pathogenesis of SIADH and basis for its management

Numerals inside figures indicate approaches to the management of SIADH: 1 – water restriction and high dietary salt intake; 2 – intravenous infusion of hypertonic (3%) saline; 3 – demeclocycline (which produces nephrogenic diabetes insipidus) or fludrocortisone with mineralocorticoid activity; 4 – nonpeptide ADH antagonists blocking V2 receptors in the kidneys (conivaptan)

Patients with SIADH have hyponatremia, volume expansion without edema (due to decreased expression of aquaporin-2) and excessive natriuresis.

Oxytocin, which is secreted from the posterior pituitary, regulates contraction of myoepithelial cells in milk ducts, producing milk ejection and stimulates myometrium contraction during parturition. No any syndromes of abnormal oxyto-

cin secretion have been described. However, brain diseases affecting ADH-producing neurons may lead to oxytocin deficiency, and in contrast, excessive administration of oxytocin for the stimulation of myometrium contraction may stimulate V2 receptors (to ADH) in the kidneys producing corresponding symptoms.

Disorders of the adrenal glands

The adrenal glands consist from the cortex and medulla and produce at least 30 hormones. There are three zones in the adrenal cortex: zona glomerulosa, zona fasciculata and zona reticularis. Zona glomerulosa is the site of aldosterone production; cortisol is produced mainly in the zona fasciculata, and zona reticularis produces adrenal androgens – dehydroepiandrosterone and dehydroepiandrosterone sulfate. Cortisol and adrenal androgens synthesis is stimulated by the ACTH, whereas aldosterone production is activated by renin. Secreted cortisol binds with cortisol-binding globulin transcortin and in less extent with albumin. Aldosterone and adrenal androgens circulate in the blood in the bind with albumin and sex hormone binding globulin (SHBG). Main roles of hormones derived from the adrenal cortex were summarized in the Table 7-1. Liver is the primary organ for the adrenal hormones degradation.

The adrenal medulla produces catecholamines (norepinephrine, epinephrine, and dopamine) from the amino acid phenylalanine, which is converted to tyrosine with subsequent synthesis of dopamine and norepinephrine. This substance is the final product in axons of sympathetic nerves, whereas in most adrenal chromaffine cells norepinephrine metabolizes to epinephrine.

Disorders of adrenal glands can be classified into congenital and acquired; due to adrenals hypofunction or hyperfunction; primary, secondary and tertiary; affecting adrenal cortex or adrenal medulla. Diseases of the adrenal cortex will be discussed further.

Congenital adrenal hyperplasia (CAH, adrenogenital syndrome)

Congenital adrenal hyperplasia is resulted from different disorders of normal adrenal steroidogenesis (Fig. 7-9).

Congenital adrenal hyperplasia is resulted from decreased activity of key enzymes of steroidogenesis in the adrenals which belong to the P-450 oxidases (21-hydroxylase, 11β-hydroxylase and 3β-hydroxysteroid dehydrogenase). As a result, synthesis of steroid hormones in the adrenal cortex disrupts at different stages and cortisol production impairs in varying degree. According with negative feedback regulation, inadequate concentrations of cortisol stimulate ACTH secretion from the anterior pituitary. In turn, ACTH stimulates adrenal cortex. Because of corresponding defects of steroidogenic enzymes result in inadequate synthesis of cortisol and/or aldosterone, ACTH is able to stimulate production of only androgens in the adrenal cortex.

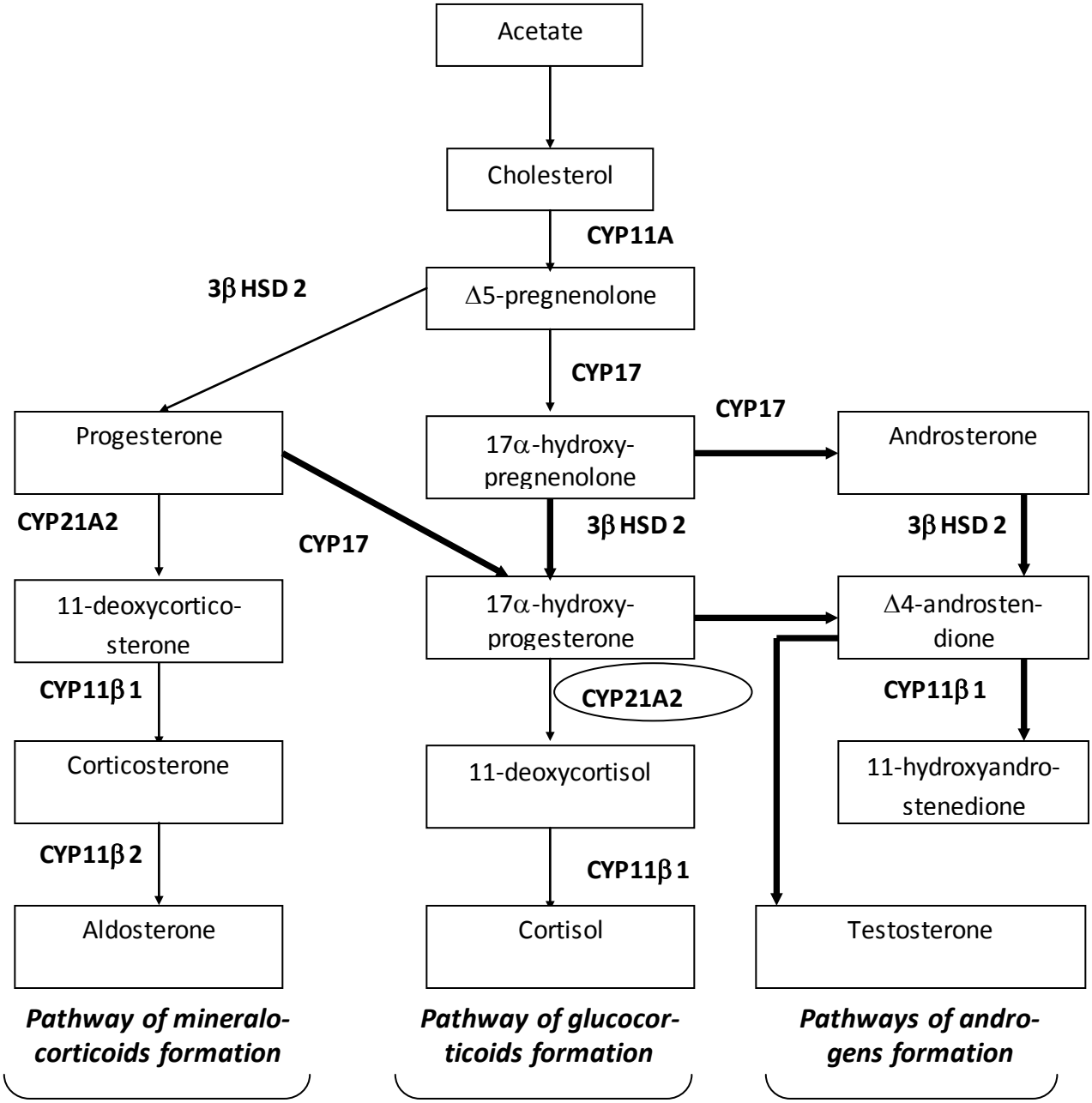


Figure 7-9. Biosynthesis of steroid hormones in the adrenal cortex (according with Williams G.H., Dluhy R.G., 2001)

CYP11A – desmolase, 3βHSD2 – 3β-hydroxysteroid dehydrogenase, CYP21A2 – 21-hydroxylase, CYP11β1 – 11β-hydroxylase, CYP11β2 – aldosterone synthase, CYP17 – 17α-hydroxylase in the reactions of 17α-hydroxypregnenolone и 17α-hydroxyprogesterone formation and 17,20-liase in the dehydroepiandrosterone synthesis. Thick arrows indicate pathway of 17-ketosteroids formation in patients with most common impairment of steroidogenesis – 21-hydroxylase deficiency.

Intrauterine exposure of adrenal androgens in the female fetus leads to alteration of fetal external genitalia with clinical symptoms of female pseudohermaph-

roditism (scrotal-like large lips of pudendum, hypospadias and clitoromegaly), whereas internal genitalia (vagina, uterus and ovarian tubes) are unaffected. Karyotype is normal female – 46,XX. Clinical signs of hyperandrogenism in mature females with CAH are summarized in the Table 7-4. Affected male fetuses have less prominent clinical signs at birth; during childhood males with CAH demonstrate premature isosexual development, during adulthood – impairment of spermatogenesis and subfertility.

Table 7-4. Clinical features related to androgens excess in females with congenital adrenal hyperplasia

Clinical signs	Mechanisms of their development
Accelerated linear growth in childhood, but decreased height in adult females	Stimulation of bone tissue growth by androgens in childhood; premature closure of epiphyseal zones in adolescents due to local aromatase-dependent conversion of androgens to estrogens in the bone tissue
Premature pubarche (pubic hair growth) in affected children	Androgen action on the hair follicles, local formation of androgens in the skin derived from DHEA
Male pattern of hair growth	Conversion of DHEA to testosterone and dihydrotestosterone in the skin and stimulation of hair follicles bulbs by androgens
Acne vulgarism which may appear even in childhood	Stimulation of sebaceous glands by adrenal androgens and locally produced their metabolites
Androgenetic alopecia	Disorders of hair growth phases by high concentrations of adrenal and locally produced androgens
Menstrual disorders (hypomenstrual syndrome or amenorrhea, oligoovulation, luteal phase insufficiency, dysfunctional uterine bleeding)	Suppression of ovarian aromatase activity by high concentrations of adrenal steroids, conversion of androgens to estrogens; impairment of pulsatile Gn-RH, FSH and LH secretion
Abnormal psychobiological status (high assertivity, masculinization, definimization, sometimes disorders of sexual orientation)	Antenatal exposure of androgens on the different cortical centers, epigenetic programming, developmental programing of behaviour
Subfertility, spontaneous miscarriages	Ovulatory disorders, luteal phase insufficiency, impairment of embryogenesis

Most common cause of the CAH is **21-hydroxylase deficiency**. It is a autosomal-recessive pathology caused by different mutations of gene CYP21, which is

located at the chromosome 6. This gene encodes 21-hydroxylase. Deficiency of the enzyme may be severe, moderate or mild. Poor 21-hydroxylase activity leads to abnormal metabolism of progesterone to 11-desoxycorticosterone and 17-α-hydroxyprogesterone to 11-desoxycortisol (See Fig. 7-9). In case of profound enzyme deficiency, aldosterone production may decrease. Concentrations of cortisol precursors – 17-α-hydroxyprogesterone, DHEA and DHEAS rise. There are three clinical forms of the 21-hydroxylase deficiency:

- Salt-wasting;
- Simple virilizing;
- Non-classical variant.

Salt-wasting form of 21-hydroxylase deficiency is resulted in severe deficiency of the enzyme. Abnormally low synthesis of both cortisol and aldosterone leads to hyponatremia, hyperkalemia, hypovolemia and arterial hypotension. Affected newborns develop severe dehydration, hypovolemic shock and acute adrenal insufficiency, which without any treatment may lead to death. Coexisting 3β-hydroxysteroid dehydrogenase deficiency causes virilization. Simple virilizing form of the 21-hydroxylase deficiency is manifested by female pseudohermaphroditism in affected female fetuses. An average frequency of the non-classical 21-hydroxylase deficiency is approximately 1:100 (1:50 among Slavs and 1:27 among Ashkenazi Jews). In fact, it is the most common hereditary autosomal-recessive pathology in humans. Non-classical 21-hydroxylase deficiency is the mildest form of the enzyme deficiency. Clinically it manifests during childhood, adolescence or even in adults during 2nd or 3rd decades of their lives. In females virilization, menstrual disorders, subfertility or recurrent spontaneous pregnancy loss (See Table 7-4) are common. Further clinical signs of hyperandrogenism in affected females may combine with hyperinsulinemia, insulin resistance, ovarian cysts formation and metabolic syndrome.

11β-hydroxylase deficiency is relatively rare cause of CAH with autosomal-recessive type of inheritance, which is due to corresponding gene mutation located at the chromosome 8. Classical form of the 11β-hydroxylase deficiency is characterized by abnormal conversion of 11-desoxycortisol to cortisol, and sometimes, 11-desoxycorticosterone to corticosterone with accumulation of these precursors with mineralocorticoid activity. Renin activity in the blood falls; hypernatremia and hyperchloremic metabolic alkalosis are common. At least 2/3 of affected patients have secondary arterial hypertension. Virilization is seen in affected patients.

Aldosterone synthase (CYP11β2) deficiency manifests by aldosterone deficiency, whereas synthesis of cortisol, progesterone and androgens is unaffected. Virilization is absent, but loss of sodium leads to severe electrolyte and acid-base disorders, which are main cause of death of affected individuals during childhood.

17α-hydroxylase and 17,20-liase (CYP17) deficiency are resulted from according gene mutation located at the chromosome 10. These enzymes participate in

the reactions of steroidogenesis both in adrenal glands and gonads normally, and their deficiency leads to impairment of cortisol, androgens, and estrogens production. Clinically the deficiency manifests by hypergonadotropic hypogonadism, arterial hypertension, hypernatremia, and hypervolemia and hypokalemic alkalosis.

3β-hydroxysteroid dehydrogenase (3βHSD2) deficiency with autosomal-recessive type of inheritance is rare, but potentially life-threatening disorder due to impairment of synthesis of steroids in the adrenal glands (See Fig. 7-9) and gonads.

Summary of CAH due to deficiency of basic enzymes of steroidogenesis are summarized in the Table 7-5.

Table 7-5. Pathophysiological characteristic of the congenital adrenal hyperplasia due to defective enzymes of steroidogenesis

Signs	Pathologies				
	21-hydroxylase deficiency	11β-hydroxylase deficiency	Aldosterone synthase deficiency	17α-oxidase deficiency	3β-hydroxysteroid dehydrogenase
Defective gene	CYP 21	CYP11B1	CYP11B2	CYP 17	HSD3B2
Prevalence in the general population	1:10-18000	1:100000	Rare	Rare	Rare
Glucocorticoids	↓	↓	N	N only corticosterone	↓
Mineralocorticoids	↓	↑	↓	↑	↓
Androgens	↑	↑	N	↓	↑
Estrogens	Relatively ↓	Relatively ↓	N	↓	↓
Blood pressure	↓	↑	↓	↑	↓
Concentration of Na^+ in the blood	↓	↑	↓	↑	↓
Concentration of K^+ in the blood	↑	↓	↑	↓	↑

Acid-base disorders	Acidosis	Acidosis or alkalosis	Acidosis	Acidosis or alkalosis	Acidosis
Elevated product in the blood serum	17α-hydroxy-progesterone	Desoxycorticosterone, 11-desoxycortisol	Corticosterone, 18-hydroxy-corticosterone	Desoxycorticosterone, Corticosterone	Dehydroepiandrosterone, 17-hydroxy-pregnenolone
Adrenal crisis	Common	Rare	Common in salt-wasting form	Uncommon	Common

↓ – Decreased; ↑ – Increased; N – Normal

Pathophysiological basis for the treatment of congenital adrenal hyperplasia: (1) glucocorticoid replacement therapy, which according with feedback mechanism suppresses ACTH secretion and androgen production in the adrenal glands; (2) mineralocorticoid replacement therapy in children who are suffering from the salt-wasting form of CAH; (3) abiraterone acetate, which blocks DHEAS synthesis; (4) reconstructive surgery if indicated; (5) psychotherapy.

Primary adrenal cortex insufficiency (primary hypocortisolism, Addison disease)

Formerly the tuberculosis of adrenal glands was the most common cause of Addison disease. Now in the developed countries it is resulted from autoimmune-mediated destruction of adrenal cortex. Sometimes autoimmune-mediated "adrenalitis" is a feature of the polyendocrine deficiency syndrome, coexisting with other autoimmune diseases such as diabetes mellitus, autoimmune thyroiditis, hypoparathyroidism and hypogonadism. Other causes (fungal infection, adrenal hemorrhage, amyloidosis, infiltrative diseases, metastasis of cancer, hemochromatosis, HIV infection, antifungal drugs) are relatively rare. Addison disease manifests by clinical and laboratory signs of glucocorticoids, mineralocorticoids and adrenal androgens (DHEAS) deficiency. However, manifestations of Addison disease usually do not become clinically significant until at least 90% of the adrenal cortex tissue has been damaged. Clinical signs of Addison disease are listed in the Table 7-6. It is important to emphasize, that clinical symptoms of secondary adrenal insufficiency, which is resulted from hypothalamic-pituitary diseases, are similar to those summarized in the Table 7-6, with one exception: patients with secondary adrenal insufficiency have not bronze-like colour of the skin, because of deficiency of ACTH and its precursor pro-opiomelanocortin. Besides that, patients with primary adrenal insufficiency will have elevated ACTH in the blood serum, in contrast to

secondary adrenal insufficiency, which is confirmed by decreased concentration of pituitary hormones including ACTH deficiency.

Table 7-6. Clinical manifestations of the primary adrenal insufficiency

Basic pathogenetic mechanisms	Consequences
Mineralocorticoids deficiency	Increased urinary loss of Na^+, Cl^- and water with decreased K^+ excretion; metabolic alkalosis, hyponatremia, hypovolemia, arrhythmia, dehydration, orthostatic hypotension, weakness, fatigue, increased salt appetite; in severe cases – cardiovascular collapse or dehydration shock
Glucocorticoids deficiency	Poor tolerance to stress, hypoglycemia, weakness, fever, anorexia, nausea, vomiting, weight loss
DHEAS deficiency	In females these syndromes are most prominent, because in males steroidogenesis in the testes compensates DHEAS deficiency; in females loss of pubic hair, sparse axillary hair, decreased libido and weakness are common
POMC excess	Stimulation of MSH production from the common precursor for the hormone and ACTH – POMC, bronze coloration of the skin

Pathophysiological basis for the treatment of Addison disease: (1) hormone replacement therapy with glucocorticoids and mineralocorticoids; (2) management of adrenal crisis – fluid replacement therapy by infusion of 0,9% saline and 5% glucose (dextrose); corticoid replacement therapy; prophylaxis of infectious complications with antibiotics.

Secondary and tertiary hypocortisolism is due to diseases affecting pituitary gland and hypothalamus, accordingly, like as neoplasms, infections, infiltrative diseases, head trauma or rare congenital conditions (See above, Disorders of the hypothalamus, Anterior pituitary disorders, ACTH hypoproduction). Today the most common cause of such hypocortisolism is a suppression of hypothalamus and corresponding ACTH secretion by exogenously administered glucocorticoids according with negative feedback regulation. Pathophysiological basis for the treatment of secondary and tertiary hypocortisolism is similar to described earlier for Addison disease.

Adrenal cortex hormone excess (Cushing's syndrome)

In contrast to Cushing's disease, which is characterized by ACTH hyperproduction, Cushing's syndrome is declared itself by hyperproduction of glucocorticoids by adrenal adenoma or carcinoma, or micronodular adrenal dysplasia, or af-

ter administration of exogenous glucocorticoids. Clinical symptoms of Cushing's syndrome are similar to those in Cushing's disease (Table 7-3).

Disorders of the adrenal medulla

Acute adrenal medulla insufficiency coexists with cortex insufficiency. It was described as **Waterhouse-Friderichsen syndrome**, which is resulted from massive hemorrhagic infarction of adrenal glands in genetically susceptible patients with meningococcal or pseudomonal septicemia. The syndrome is characterized clinically by profound arterial hypotension, shock, and disseminated intravascular coagulation.

Excessive production of catecholamines in the adrenal medulla due to pheochromocytoma was discussed in the Part II – 3 ("Disorders of regulation of vascular tone. Arterial hypertension. Arterial hypotension).

Thyroid gland disorders

The thyroid gland is the largest endocrine gland in the human body, which is controlled by hypothalamic and anterior pituitary feedback mechanisms. Thyroid gland consists from multiply follicles, which contain colloid inside. Follicular cells collect iodine, which daily absorption is approximately 150-200 μg, transport iodine to the colloid via ATPase-dependent Na^+/I^- symporter, synthetize thyroglobulin and release of thyroid hormones from thyroglobulin after TSH stimulation. Steps of thyroid hormone synthesis are following: (1) oxidation of iodide by thyroid peroxidase (TPO) or "organification" of iodide; (2) synthesis of monoiodotyrosine; (3) formation of diiodotyrosine; (4) synthesis of thyroxine (T_4); (5) combination of monoiodotyrosine with diiodotyrosine with formation of thyroxin (T_3). Thyroid gland releases approximately 90% of T_4 and only 10% of T_3, whereas most circulating T_3 derives from the peripheral conversion $T_4 \rightarrow T_3$ by peripheral deiodinases. Deiodinases also may produce rT_3 (reverse T_3) from the 40-50% of the total peripheral T_4. It is known, that rT_3 is a competitive inhibitor of T_3 at the cellular level; moreover, it suppresses deiodinases activity. Most peripheral effects of thyroid hormones are mediated by T_3. In the blood thyroxine binds to thyroxine-binding globulin, transthyrein and albumin. Only free thyroid hormones are active (in the blood only 0.03% of T_4 is free). The half-life of T_4 is approximately 6-7 days; the half-life of T_3 is only 1 day; that is why T_4 is more appropriate marker to assess adequacy of hormone-replacement therapy in patients with chronic hypothyroidism. Thyroid hormones possess both classical genomic and non-classical non-genomic action. Genomic action of thyroid hormones is based on their ability to bind with nuclear thyroid hormone receptors and interact with thyroid response elements in DNA. Such receptors bind with DNA as homodimers or heterodimers (with retinoic X receptors) with stimulation or inhibition of target genes. Thyroid hormones enhance metabolic rate, cellular differentiation and growth. Almost all cells in systems and organs are regulated by thyroid hormones. Thyroid hormones are metabolized via deiodination, glucuronidation, binding with sulfuric acid, de-

amination, and decarboxylation and bile excretion. Non-classical action of thyroid hormones is explained by their ability to activate different protein kinases.

Disorders of thyroid gland clinically manifest as hyperthyroidism or hypothyroidism. These disorders may be hereditary or acquired; primary, secondary or tertiary.

Hyperthyroidism

Hyperthyroidism is a hyperfunction of the thyroid gland, which produces excessive amounts of thyroid hormones. In such high concentrations thyroid hormones over stimulate multiply cells, causing typical biological response – thyrotoxicosis. Hyperthyroidism can be overt (with clinical signs of hyperthyroidism, elevated T_3 and T_4 and altered TSH level) or subclinical (without clinical signs, normal thyroid hormones and slightly abnormal TSH). Causes of hyperthyroidism are following:

A. Primary hyperthyroidism:
   - Stimulation of thyroid hormones production by stimulating TSH-like antibodies (Graves' disease);
   - Toxic adenoma, toxic nodular goiter or cancer of the thyroid gland, producing excess of thyroid hormones ;
   - Iodine-induced hyperthyroidism;
   - Stimulation of thyroid hormones release in painful subacute thyroiditis, painless lymphocytic thyroiditis.

B. Secondary hyperthyroidism:
   - Stimulation of the thyroid gland by excessive TSH, secreting by pituitary tumors;

C. Stimulation of thyroid gland by human chorionic gonadotropin (hCG) in patients with choriocarcinoma or hydatiform mole, because of TSH and hCG have common identical subunit;

D. Ectopic production of TSH and/or thyroid hormones as a sign of paraneoplastic syndrome.

Most common cause of hyperthyroidism is **Graves' disease**, a multifactorial organ-specific autoimmune disease which predominantly affects females. The latter is explained by sex steroids-dependent regulation of immune cells and inactivation of X-chromosome in female with epigenetic regulation of genes involved in the immune regulation. Pathogenesis of Graves' disease is simplistic illustrated in the Fig. 7-10.

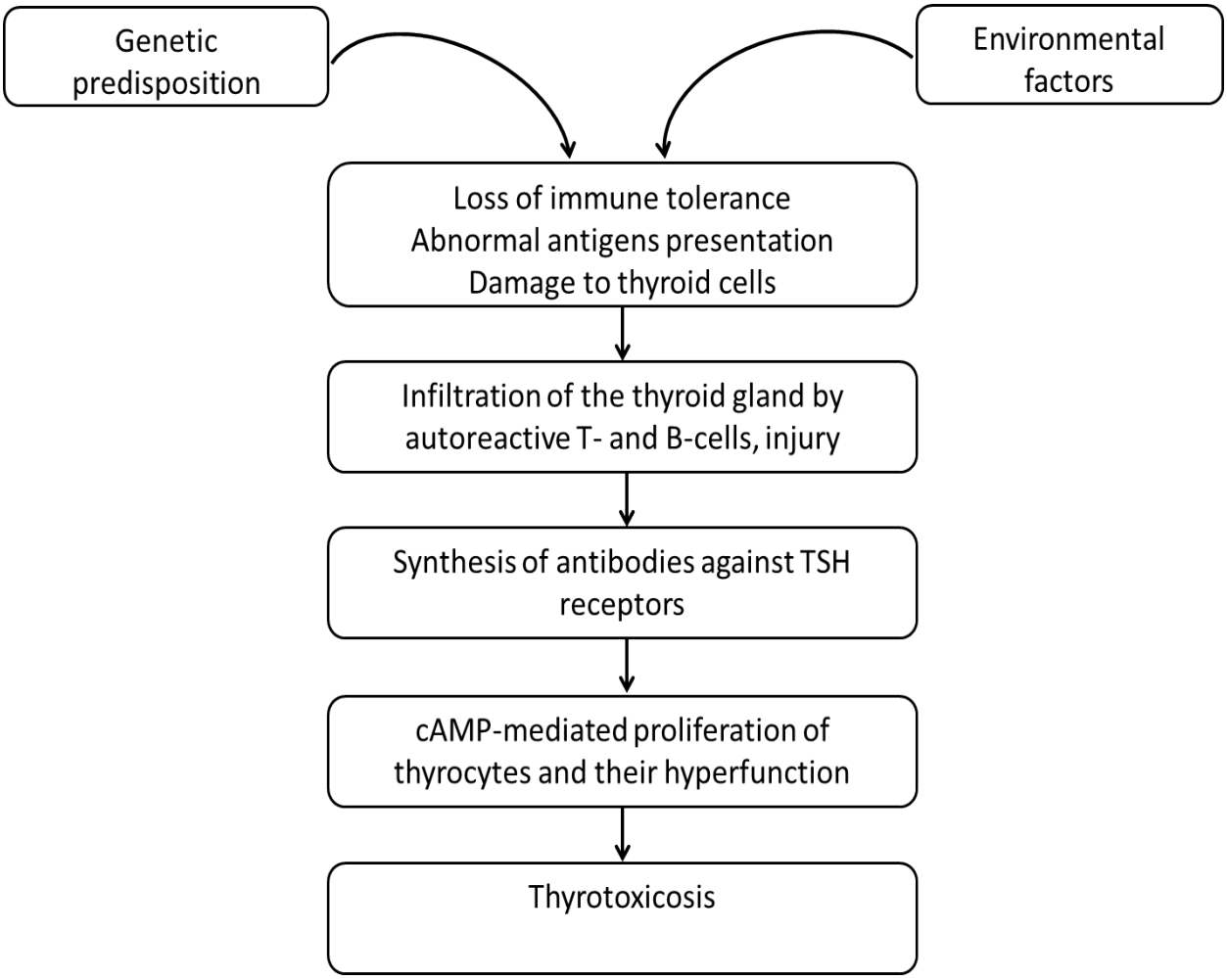


Figure 7-10. Pathogenesis of Graves' disease

Genetic predisposition to autoimmune thyroiditis means presence of specific MHC II class genes in genetically susceptible individuals as other genes-candidates (**a**uto**i**mmune **re**gulator (AIRE) gene, **c**ytotoxic **T**-**l**ymphocytes **a**ssociated factor 4 gene (CTLA4), CD 40 gene, CD 25 gene, tyrosine phosphatase gene, cytokine regulatory genes and many other genes). Environmental factors (infections, especially viral, diet, intake of iodine, alcohol, smoking, selenium deficiency, some drugs like as amiodarone, propranolol, NSAIDs, corticosteroids, IFN-α) produce primary injury of the thyroid gland and disorders of immune regulation with disbalance Th1/Th2/Th17/T-regulatory cells with abnormal recognition and presentation of novel or cryptic antigens by APCs result in recruitment of lymphocytes in the thyroid, their activation and secondary injury of the thyroid gland with releasing of cryptic antigens and potentiating of an autoimmune process. Activation of B-cells results in synthesis of antibodies against receptors to TSH. Such autoantibodies may be stimulating, inhibiting or neutral. Stimulating autoantibodies trigger proliferation of thyrocytes and their hyperfunction even without TSH through activation of adenylate cyclase and cAMP. As a result, thyrotoxicosis develops (Table 7-7).

Table 7-7. Clinical symptoms of Graves' disease and their mechanisms

Systems and organs	Changes	Pathogenesis
Central nervous system	Nervousness and emotional lability	Neurons dysfunction, disorders of neurotransmitter metabolism
Cardiovascular system	Palpitations, tachycardia, atrial fibrillation, increased pulse pressure	Permissive action of thyroid hormones on catecholamines release and action, ↑ CO, peripheral vasodilation. Pathogenesis of arrhythmia: (1) increased expression of SERCA in the pacemakers of sinus node; (2) increased expression of β-adrenoreceptors; (3) elevated activity of Na^+/K^+ATPase and voltage-gated K^+-channels; (4) decreased activity of $Na^+/Ca2^+$ATPase; (5) increased sympathetic nervous system tone result in decrease in diastolic membrane potential in the major pacemakers, increase velocity of spontaneous diastolic depolarization, "re-entry" mechanism and activation of ectopic pacemakers.
Gastrointestinal tract	Hyperdefecation, gastrointestinal hypermotility, diarrhea, gastric juice hypersecretion	Disorders of gastrointestinal smooth muscular cells due to thyroid hormone excess
Muscle system	Proximal muscle weakness, muscle atrophy, hyperreflexia	Increased protein catabolism, disorders of neuromuscular transmission
Eyes	Graves' ophthalmopathy (widened palpebral fissure, periorbital edema, proptosis, chemosis, and conjunctival ejection)	"Molecular mimicry", when self-reactive lymphocytes recognize an orbital antigens as thyroid antigens; infiltration of periorbital space with lymphocytes and fibroblasts, excessive synthesis of glycosaminoglycans

Skin	Warm moist smooth skin, onycholysis, fine hair, hair loss, excessive perspiration, pretibial myxedema	Dermopathy due to excess thyroid hormones
Metabolism	Heat intolerance, weight loss, increased appetite	Catabolism accelerates due to thyroid hormones excess
Thyroid	Enlargement of nodules, goiter	Increased follicular cells proliferation rate
Reproductive system	Menstrual disorders in females, decreased libido	Stimulation of estrogen receptors expression by T_3, stimulation of estradiol production, hyperproduction of sex steroids binding globulin with androgens deficiency

Pathophysiological basis for Graves' disease treatment: (1) antithyroid drugs to reduce hyperproduction of thyroid hormones – methimazole and its analogs, which inhibit thyroid peroxidase activity and suppress synthesis of thyroid hormones; (2) radioactive iodine to inhibit hyperproduction of thyroid hormones; (3) surgery – subtotal thyroidectomy; (4) β-adrenoblockers to abolish cardiovascular effects of thyroid hormones excess.

Hypothyroidism

Hypothyroidism is a hypofunction of the thyroid gland with deficiency of thyroid hormones. Hypothyroidism can be classified into overt (with clinical signs of hypothyroidism, decreased T_3 and T_4 and altered TSH level) or subclinical (without clinical signs, normal thyroid hormones and slightly elevated TSH). Hypothyroidism may be congenital (hereditary or non-hereditary) or acquired; primary, secondary or tertiary. Most genetic disorders of congenital hypothyroidism have autosomal recessive type of inheritance with relatively small number of autosomal dominant diseases. Any part of hypothalamic-pituitary-thyroid axis may be impaired in congenital hypothyroidism. Acquired primary hypothyroidism is a most common form of hypothyroidism (90-95% of all thyroid hypofunction causes). Etiology of primary hypothyroidism is following:

1. Insufficient amount of thyroid tissue (thyroiditis, after radiation exposure, surgical thyroidectomy, infiltrative diseases);
2. Defects of thyroid hormone biosynthesis due to congenital enzyme defects; congenital mutations of TSH receptors; iodine deficiency; drug-induced (thionamides, lithium salts, sulfonamides, overdose of iodine); action of some proinflammatory cytokines.

Secondary hypothyroidism may be detected as a part of panhypopituitarism

due to neoplasms, radiation, surgery, Sheehan's syndrome or isolated TSH deficiency. Tertiary hypothyroidism is resulted from different hypothalamic disorders (congenital, infectious diseases, infiltrative diseases, vascular diseases and neoplasms).

Generalized resistance to thyroid hormones is a rare cause of hypothyroidism. The latter is an autosomal dominant disorder resulted from mutation of gene encoding thyroid hormone receptor β subunit, clinical signs of hypothyroidism and normal or elevated TSH concentration.

Most common cause of primary hypothyroidism is **Hashimoto's thyroiditis**, which affects predominantly females (females to males ratio is approximately 5:1). Together with Graves' disease it is related to autoimmune thyroid disease. To better understand of pathogenesis of the disease it is desirable to repeat Part XIV "Autoimmune diseases. Immunodeficiencies" in the Textbook "General pathophysiology: the essentials". Genetic predisposition and environmental factors result in loss of immune tolerance, damage of the thyroid gland, with releasing of auto-antigens, which after their recognition by antigen-presenting cells are presented to autoreactive T-cells. Polarization of immune response towards Th1 favors cellular-mediated immune reaction. Cytotoxic lymphocytes mediate Fas-L induced apoptosis of thyroid cells. Activated B-cells transform into plasma cells, which produce antibodies against thyroid peroxidase, thyroglobulin and protein pendrin, which transports iodine into colloid of follicles. Thyroid gland is infiltrated by lymphocytes, which produce proinflammatory cytokines promoting further injury of the thyroid gland. As a result of normal thyroid tissue deficiency, clinical signs of hypothyroidism appear (Table 7-8).

Table 7-8. Clinical symptoms of hypothyroidism

Systems and organs	Changes	Pathogenesis
Central nervous system	Forgetfulness, stoic appearance, myxedematous dementia, cerebellar ataxia	Neurons dysfunction, disorders of neurotransmitter metabolism
Cardiovascular system	Bradycardia, pericardial effusion, arterial hypertension, higher risk of coronary artery disease	Interstitial myxedema, ↑ systemic vascular resistance, vascular stiffness due to accumulation of glycosaminoglycans in the vascular wall, endothelial dysfunction, hypercholesterolemia

Gastro-intesti-nal tract	Constipation, hypomotility, paralytic ileus, gastric juice hyposecretion	Disorders of gastrointestinal smooth muscular cells due to thyroid hormone deficiency
Muscle system	Delayed tendom reflexes, muscle stiffness and cramps, increased muscle volume weakness	Absence of permissive action of thyroid hormones on muscular cells
Skin	Dry, rough, pain, cool, hyperkeratosis, edema of hands and feet (myxedema), enlarged tongue, ecchymosis, slow wound healing	Accumulation of proteoglycans and water, skin vessel vasoconstriction, increased capillary fragility
Meta-bolic	Basal metabolic rate decreased, cold intolerance, decreased T4 and drug turnover, weight gain	Thyroid hormone deficiency, lack of intracellular process stimulation; fluid retention
Thy-roid	Goiter or atrophy	Goitrous variant is most common in individuals with HLA-DR5, whereas atrophic variant is more specific for HLA-DR3 positive patients Thyroid enlargement may be caused by stimulating antibodies against receptors to TSH
Repro-ductive system	Menstrual disorders in females (oligoovulation, hypomenstrual syndrome, menorrhagia, insufficiency of luteal phase of the menstrual cycle, subfertility, complications of pregnancy, decreased libido	Disorders of hypothalamic and pituitary hormones synthesis in hypothyroid patients, impaired action and metabolism of sex steroids, abnormal function of gonadal cells, TSH-mediated hyperprolactinemia

Pathophysiological basis for Hashimoto's thyroiditis treatment: (1) to achieve euthyroid state thyroxine replacement is necessary; (2) surgery in severe thyroid gland enlargement with subsequent hormone-replacement therapy.

Other forms of thyroiditis manifesting by hypothyroidism include acute suppurative thyroiditis, late stage of subacute painful (granulomatous) thyroiditis, drug-induced thyroiditis and fibrous thyroiditis (Riedel's thyroiditis).

Nonthyroidal illness syndrome (sick euthyroid syndrome) is a clinical and laboratory syndrome, which is characterized by decreased concentration of T_3 and sometimes T_4, increased rT_3 without underlying disorder of the thyroid gland. Etiology of nonthyroidal sick syndrome includes severe critical illness, psychical trauma, posttraumatic stress disorder, and severe malnutrition, which are characterized by oxidative stress, activation of ACTH-cortisol axis and hyperproduction of proinflammatory cytokines. Basic pathogenetic mechanisms of the syndrome are following: (1) decrease activity of peripheral deiodinases; (2) lack of TSH production; (3) rise in thyroid hormones-binding proteins production. Sick euthyroid syndrome may worse prognosis of the underlying disease. Thyroid-replacement therapy of this syndrome is controversial.

Disorders of iodine consumption as a cause of thyroid gland hypofunction or hyperfunction

Iodine deficiency is now recognized as a global problem affecting individuals living in regions with lack of iodine in the soil (far from seas or oceans). Endemic goiter affects approximately 10% of a population of the globe. Oversimplified, pathogenesis of endemic goiter can be presented as following: dietary iodine deficiency → lack of thyroid hormones → stimulation of TSH secretion → hypertrophy and hyperplasia of thyroid epithelial cells → endemic goiter. Moreover, follicular cells express more Na^+/I^- symporter, and produce more thyroglobulin. Clinically endemic goiter manifests by thyroid enlargement and clinical signs of hypothyroidism (See Table 7-8). Iodine deficiency may adversely influence on the pregnant females and their fetuses. Fetal thyroid ontogeny starts from 10-12 weeks of gestation and is not complete until delivery; fetal T_4 is not secreted until 18-20 weeks of gestation. Before this time the fetal brain is dependent on the circulating maternal T_4. Maternal hypothyroidism associates with increased risk of miscarriage and perinatal mortality; high risk of low birth weight, preterm birth, fetal distress, and impaired mental and somatic development in the postnatal period. Maternal iodine deficiency following 12-30 weeks of pregnancy is manifested by neurologic cretinism in her child, which is caused by reduced brain weight, disorders of neurons formation, differentiation and synaptogenesis and manifested by severe mental deficiency, neuromotor defects, spastic diplegia and delayed growth. Myxedematous endemic cretinism is a more silent form of maternal and postnatal iodine deficiency (Fig. 7-11).

Prevention and management of endemic goiter are required iodization of salt and administration of iodine (KI).

However, iodine overdosage may lead to iatrogenic hyperthyroidism. It is also important to note, that iodine administration may result in iodine-induced hypothyroidism. Acute intake of iodine provokes transient, at least during 24 hours, reduction of thyroid hormone synthesis (Wolff-Chaikoff effect). This effect is based on the stimulation by iodine formation of iodolactones, iodoaldehyds and iodolipids in the thyroid gland, which inhibit thyroid peroxidase activity and thus

diminish synthesis of thyroid hormones. Regularly overdosage also suppresses expression of Na^+/I^- symporter in the thyroid follicular cells. In patients with autoimmune thyroid disease iodine overconsumption may produce hypothyroidism via several mechanisms: (1) iodine stimulates lymphocytic infiltration of the thyroid gland and increases synthesis of proinflammatory cytokines and chemokines thus enhancing inflammation in the thyroid gland; (2) iodine stimulated oxidative stress in the thyroid gland with tissue injury and releasing of cryptic self-antigens; (3) iodine activates MHC II molecules expression and causes thyroglobulin iodination thus facilitating self-antigens presentation thus augmenting autoimmune process in the thyroid gland.

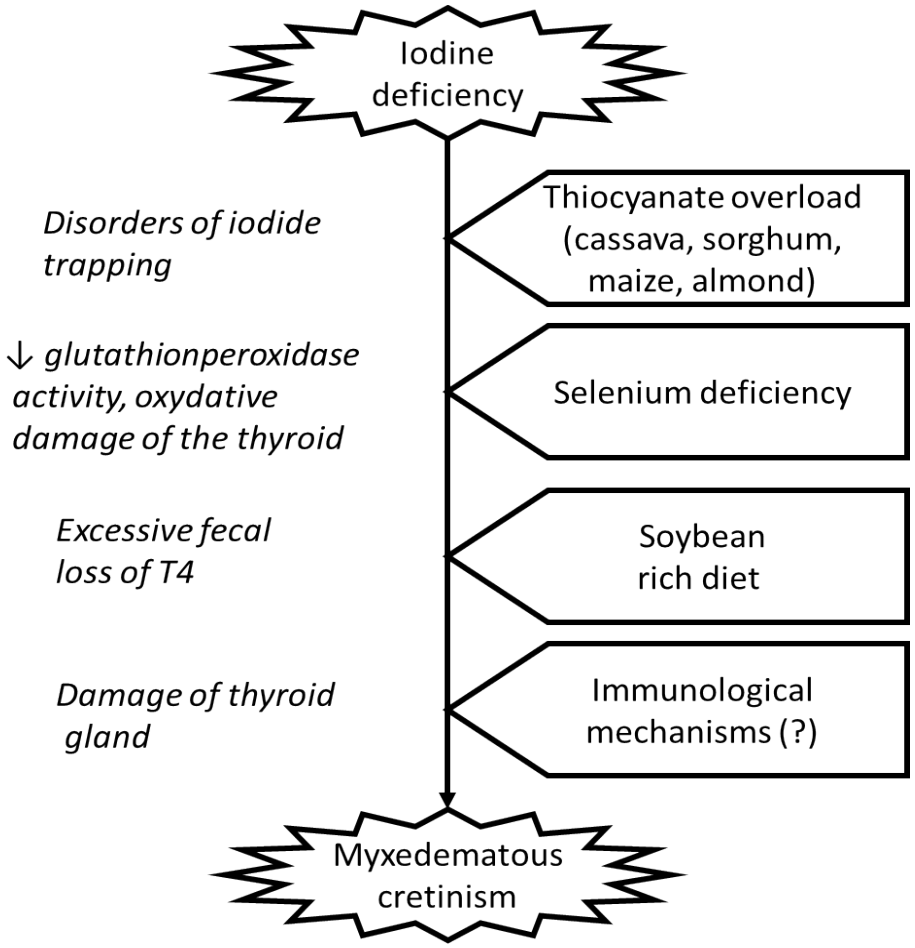


Figure 7-11. Pathogenesis of myxedematous cretinism

Disorders of the parathyroid glands

The four parathyroid glands are composed of chief cells, clear cells and oxyphil cells. In response to decrease ionized calcium level in the blood chief cells having plasma G protein-coupled membrane calcium receptors produce peptide parathyroid hormone (PTH), whose net result is an increase of the level of ionized calcium in the blood. It is important to note, that calcium in biological fluids exists in several forms: ionized, protein-bound (with albumin and globulins) and complexed with citrate, phosphate and bicarbonate. Only ionized (free) calcium con-

trols multiply cellular functions.

Main function of PTH is a regulation of calcium homeostasis together with vitamin D (Fig. 7-12).

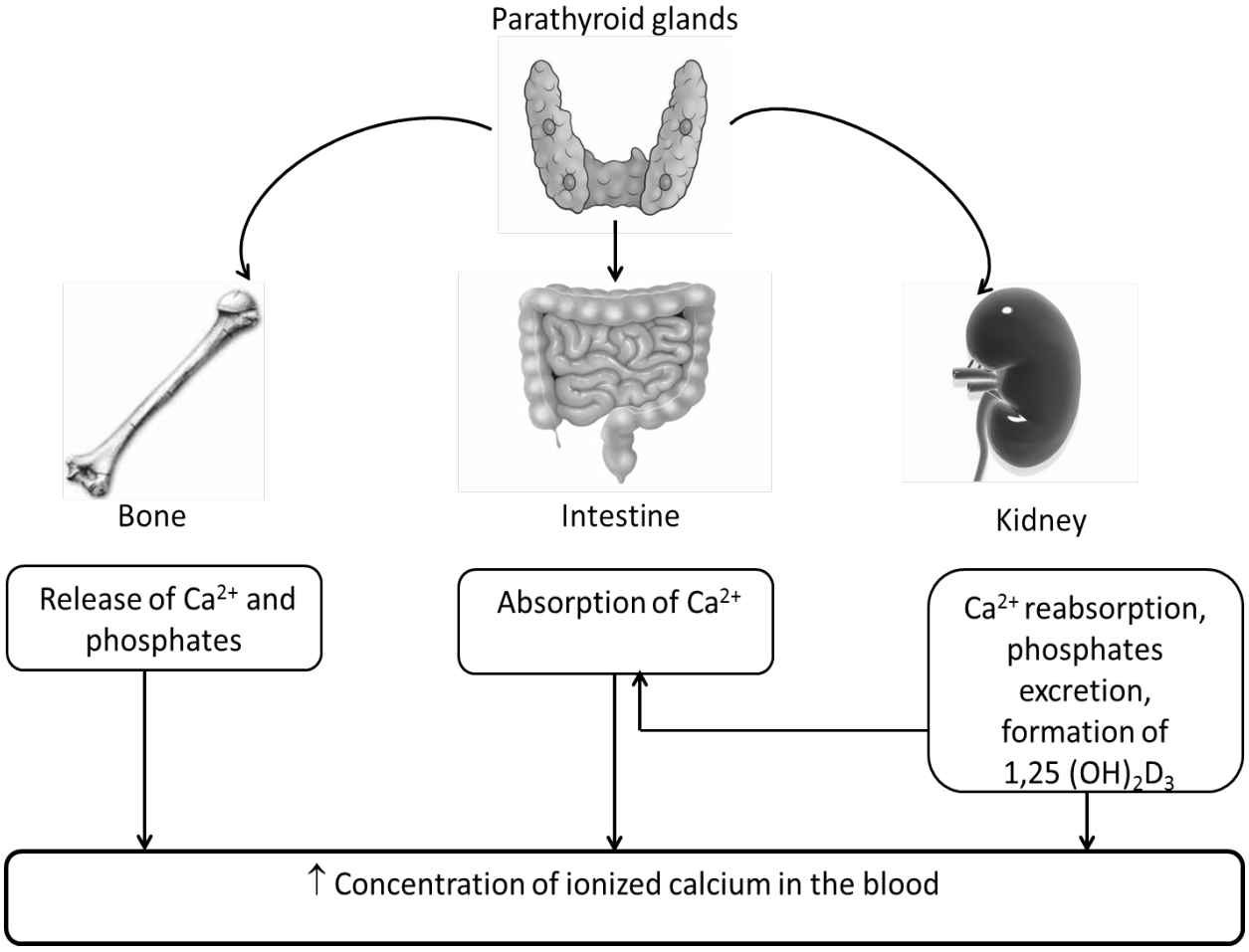


Figure 7-12. Simplified mechanism of PTH action

Complex regulation of calcium homeostasis is achieved via action of PTH, calcitonin produced by parafollicular cells (C cells) of thyroid gland and vitamin D (Table 7-9).

Table 7-9. Influence of the TTH, calcitonin and vitamin D on the calcium homeostasis

Mechanism of action	PTH	Calcitonin	Vitamin D
Absorption of calcium in the intestine	↑ due to action of vitamin D	~	↑
Absorption of phosphates in the intestine	↑	~	↑

Renal calcium excretion	↓	Non-significant	↑
Renal phosphates excretion	↑	Non-significant	↑
Bone resorption	↑	↓	↑ by $1,25(OH)_2D_3$
Bone formation	↓	Uncertain	↑ by $24,25(OH)_2D_3$
Ionized calcium level in the blood	↑	↓	~
Phosphates level in the blood	Prevention of ↑	↓ by pharmacological doses	~

↑ - increase, ↓ - decrease, ~ - not affected.

Abnormalities of the parathyroid glands are characterized by hyperparathyroidism or hypoparathyroidism.

Hyperparathyroidism

Hyperparathyroidism is characterized by increased PTH secretion. It can be classified into primary, which is due to disorders of the parathyroid glands, and secondary, which is related to other underlying disorders.

Most common causes of primary hyperparathyroidism are primary parathyroid adenomas, parathyroid hyperplasia or relatively rare hereditary syndromes with autonomous PTH hypersecretion. Female to male ratio of patients with primary hyperparathyroidism is approximately 3:1. Adenomas most commonly affect inferior parathyroid glands. Cells of parathyroid adenomas have a proliferative potential, which is higher than in normal cells due to activity of PRAD1 gene encoding cyclin D1. Primary hyperparathyroidism also may be a part of the multiply endocrine neoplasia (MEN) syndrome with autosomal-dominant type of inheritance. MEN1 encodes tumor suppressor menin, which interacts with different proteins involved in transcriptional regulation, genome stability, cell division and cellular proliferation.

Clinical signs of MEN 1 include hyperplasia or parathyroid adenoma, pituitary neoplasms, pancreatic tumors and sometimes – Zollinger-Ellison syndrome with HCl hypersecretion and peptic ulcer disease. Similar to MEN 1, MEN2A is characterized by parathyroid adenoma, but also by pheochromocytoma, and medullary carcinoma affecting thyroid gland. Other mutated genes in patients with primary hyperparathyroidism are CASR (encoding calcium-sensing receptor), HRPT2, RET and some others. Parathyroid carcinoma is relatively rare cause of primary hyperparathyroidism. In all cases of hyperparathyroidism chief cells gradually loss their sensitivity to serum calcium level.

Currently up to 80% of patients with primary hyperparathyroidism are asymptomatic. Diagnosis of hyperparathyroidism is based on persistent hypercalcemia and elevated or normal PTH. However, normocalcemic variant of prima-

ry hyperparathyroidism was evaluated. Clinical features of hyperparathyroidism are summarized in the Table 7-10.

Table 7-10. Clinical symptoms of PTH hyperproduction

Organs and systems	Changes
Bones	Osteitis fibrosa cystica ("a salt-and-pepper" appearance in the skull, phalangeal subperiostal bone resorption, cysts, bone pain, skeletal deformities, pathological fractures)
Kidneys	Nephrocalcinosis, nephrolithiasis, hypercalciuria
Muscles and peripheral nervous system	Muscle weakness, peripheral polyneuropathy
Cardiovascular system	Arterial hypertension due to increased vascular stiffness, left ventricle hypertrophy, valve calcification, atherosclerosis, cardiac arrhythmias
Gastrointestinal tract	Peptic ulcer (commonly associated with MEN due to gastrinoma), pancreatitis
Central nervous system	Anxiety, irritability, apathy, psychosis, loss of memory

Pathogenesis of osteitis fibrosa cystica can be explained by abnormal interaction of RANKL (**R**eceptor **A**ctivator of **N**uclear factor **K**appa B **L**igand) / RANK / osteoprotegerin, members of tumor necrosis factor family (Fig. 7-13).

Symptomatic hypercalcemia manifests by nausea, vomiting, and short QT interval on the ECG.

Secondary hyperparathyroidism may be resulted from different causes:

- Poor intestinal calcium absorption (due to vitamin D deficiency, bariatric surgery, malabsorption syndrome, and inadequate calcium intake);
- CKD with estimated GFR less than 60 ml/min. or after use of loop diuretics with resultant hyperphosphatemia and inadequate formation of $1,25(OH)_2D_3$, which lead to hypocalcemia and corresponding PTH hyperproduction;
- Hungry bone syndrome developing after parathyroid surgery for symptomatic primary hyperparathyroidism;
- Pseudohypoparathyroidism, which is characterized by high PTH level and hypocalcemia due to PTH resistance;
- Drug-induced (caused by lithium drugs, hydrochlorothiazide, anticonvulsants, and bisphosphonates.

Pathophysiological basis for primary hyperparathyroidism treatment: (1) surgery; (2) bisphosphonates (alendronate) to maintain bones integrity; (3) calcimimetics (cinacalcet) to stimulate activity of calcium-sensing receptors.

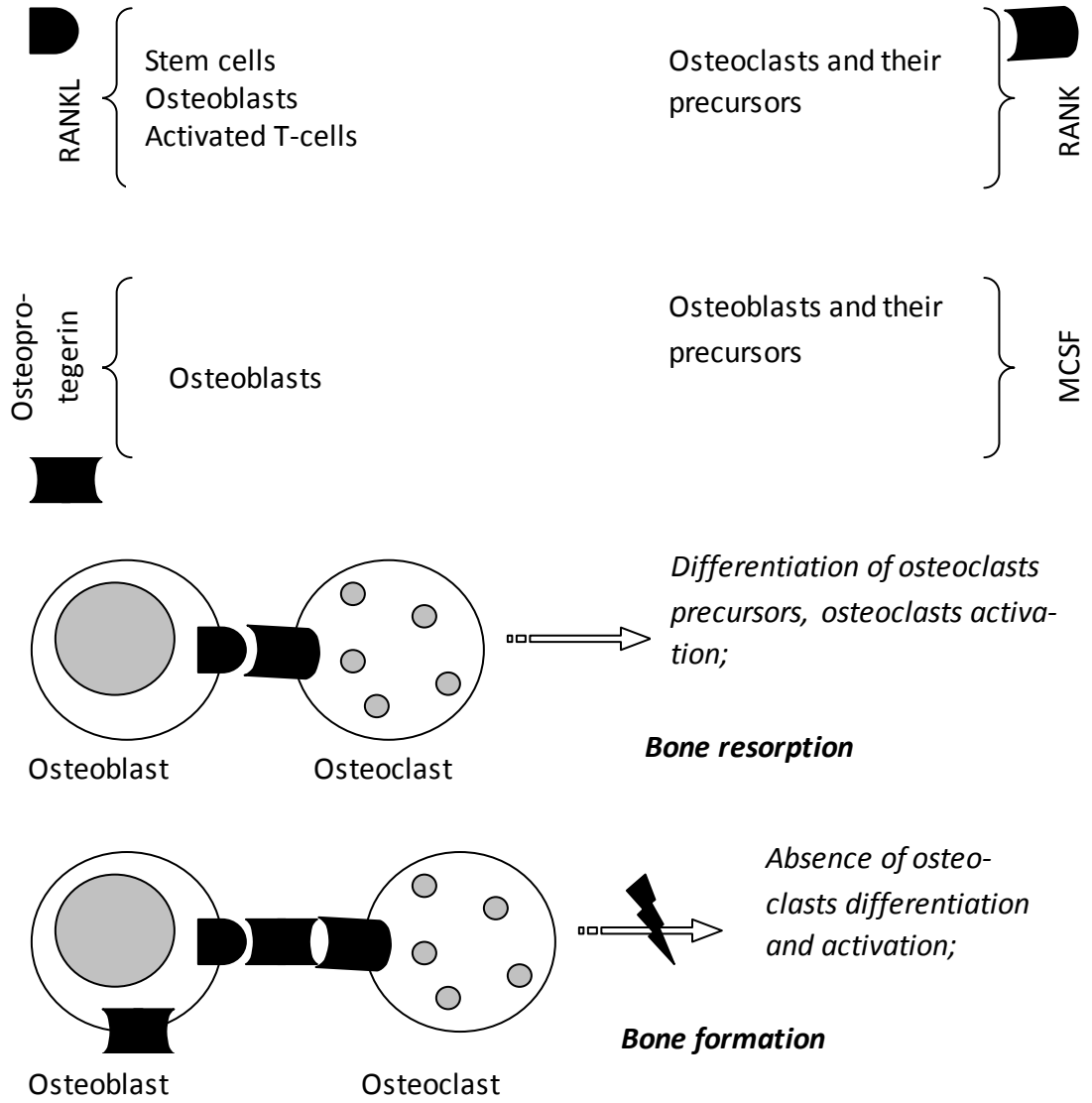


Figure 7-13. System of RANKL / RANK / osteoprotegerin

PTH regulates the expression of the receptor activator of nuclear factor-κB (RANK) ligand (RANKL) in osteoblasts , and its soluble decoy receptor osteoprotegerin, which both play a dominant role in osteoclastogenesis. RANKL binds to the RANK on the surface of hematopoietic precursors of osteoclast, promoting their differentiation and survival. Osteoprotegerin directly binds with RANKL and prevents RANKL/RANK interactions. In case of hyperparathyroidism, RANKL expression increases, whereas expression of osteoprotegerin falls with accelerated bone resorption.

Hypoparathyroidism

Hypoparathyroidism is a state of insufficient production and/or action of PTH. The example of inborn hypoparathyroidism is the DiGeorge's syndrome, which is characterized by the thymus and parathyroid glands hypoplasia and primary immunodeficiency. Relatively rare causes of idiopathic hypoparathyroidism

are based on gene mutations in the PTH gene with inadequately low PTH synthesis or activating mutation of gene encoding calcium-sensing receptor. The most common cause of acquired hypoparathyroidism is a surgical resection of the thyroid gland, because of parathyroid glands may be located into the thyroid gland. Other acquired causes of hypoparathyroidism include some metabolic diseases (hemochromatosis, iron overload in thalassemia, Wilson's disease) and autoimmune diseases with damage of parathyroid glands.

Inadequate action of normal or even elevated PTH concentrations was termed as pseudohypoparathyroidism (Albright's hereditary osteodystrophy). The type I of the disease is resulted from autosomal dominant mutation leading to deficiency of Gs-protein coupled with PTH receptor (and also TSH receptor and gonadotropins receptors) with adenylyl cyclase. As a result, cAMP synthesis fails to activate these receptors, and patients develop not isolated hypoparathyroidism, but also hypothyroidism and hypogonadism as a short stature, obesity, mental retardation and some congenital anomalies of skeleton.

Hypoparathyroidism manifests by clinical signs of hypocalcemia: increased neuromuscular excitability, paresthesias, muscle cramping, carbopedal spasm, laryngeal stridor, and convulsions. However, patients with chronic severe hypocalcemia demonstrate few symptoms. Cardiac effects of hypocalcemia include prolonged QT interval on ECG and sometimes clinical signs of heart failure. Long-term hypocalcemia may lead to dental caries and bone abnormalities.

Pathophysiological basis for hypoparathyroidism treatment: (1) in case of acute hypocalcemia – intravenous calcium infusion; (2) in chronic forms – lifelong treatment with vitamin D and oral calcium supplementation.

Endocrine disorders of gonads

Endocrine testicular disorders

In general, male endocrine function is a part of the axis including besides testes, the central nervous system, hypothalamus, pituitary, organs sensitive to sex steroids and organs of sex steroids metabolism. The male testis is a site of male sex steroids and sperm production. Most important components of testis are seminephrous tubules composed from Sertoli cells, germ cells at any stage of differentiation, interstitium with synthesizing sex steroids Leydig cells. The principal male hormone is testosterone, whose synthesis is stimulated by LH; however, androstenedione and dihydrotestosterone are also produced by testes. Testosterone acts on the target organs directly and after peripheral conversion to more active metabolite dihydrotestosterone (DHT) by 5α-reductase. Testosterone also is metabolized to estradiol by aromatase. Testosterone plays an important role in male organism: during intrauterine development it regulates differentiation of the internal and external genitalia, in the postnatal period it determines development and secondary male characteristics. Testosterone stimulates skeletal growth and muscles development; it promotes protein synthesis and induces erythropoiesis, provides changes of the larynx with deep male voice, and stimulates activity of sebaceous glands in

the skin.

Spermatogenesis is under multiple control mediated by FSH, androgens, and paracrine acting growth factors, cytokines, activin and inhibin. When spermatogenesis is finished, spermatozoa are released into the excretory system.

Male hypergonadism

Male hypergonadism is due to hyperproduction of male androgens. It can be classified into hereditary and acquired; primary, secondary and tertiary. If androgen excess is seen before puberty, it manifests by precocious isosexual puberty (before age 9). Causes of precocious puberty can be subdivided into gonadotropins-dependent (related to idiopathic precocious puberty, hypothalamic tumors, inflammatory diseases and tumors affecting CNS) and gonadotropins-independent (due to congenital adrenal hyperplasia, See before; chorionic gonadotropin-secreting tumors, exogenously prescribed androgens and McCune-Albright syndrome). If androgen hyperproduction starts after puberty, it is characterized by lack of clinical signs, except subfertility; because of increased testosterone concentrations suppress gonadotropin production with impairment of spermatogenesis.

Pathophysiological basis for male hypergonadism treatment: (1) management of underlying disorder; (2) GnRH analogues to suppress gonadotropins and testosterone production before puberty; (3) inhibitors of steroidogenesis in case of gonadotropins-independent hypergonadism: ketoconazole, androgen receptors antagonists (spironolactone and more potent), and aromatase inhibitors.

Male hypogonadism

Male hypogonadism is characterized by low circulating level of testosterone. Depending on the level of any abnormalities in hormonal secretion regulation, it can be classified into primary (due to diseases affecting testis), secondary (due to inadequate secretion and/or action of FSH and/or LH) and tertiary (due to hypothalamic disorders). Some causes for secondary and tertiary hypogonadism are seen in the current Part of the Textbook. More detailed etiology of primary male hypogonadism will be discussed further. Depending on FSH and LH blood concentration, hypogonadism may be hypogonadotropic or hypergonadotropic.

Primary hypogonadism may be congenital or acquired. Leydig cell aplasia is an example of congenital hypogonadism, which is due to gene mutations encoding of receptor to LH. It is characterized by the absence of virilization, increased LH and normal FSH concentration, increased level of antimülerian hormone (AMH) and low testosterone with infertility or without it. Other forms of primary hypogonadism in male include 5α-reductase deficiency, androgen insensitivity syndrome, persistent mülerian duct syndrome and some others. 5α-reductase deficiency is a rare autosomal recessive disease, which is characterized by normal or even elevated testosterone in the blood, but decreased DHT with selective impairment of male sex differentiation, for instance, presence of ambiguous genitalia. Affected individuals have a female habitus and delayed masculinization during puberty.

Androgen insensitivity is based on mutations of X-linked genes encoding androgen receptor with clinical signs of male pseudohermaphroditism. Persistent mülerian duct syndrome is a rare autosomal recessive disorder with isolated deficiency of AMH which leads to presence of uterus with tubes in normally virilized males. The syndrome is based on mutations of receptor to AMH. Developmental disorders, for instance, prenatal diethylstilbestrol or endocrine disrupting chemicals exposure may also lead to male hypogonadism via epigenetic regulation of genes which are responsible for androgens synthesis, metabolism and action.

Klinefelter syndrome (44, XXY), which is resulted from nondisjunction and the additional X chromosome is also characterized by hypergonadotropic hypogonadism. Affected males are infertile. Poor facial hair growth, tall stature, gynaecomastia and decreased IQ are common signs of the syndrome.

Acquired causes of primary hypogonadism are resulted from testes injury caused by different pathogens:

- Viruses and bacteria;
- Infiltrative diseases affecting hypothalamus or pituitary gland, or gonads;
- Trauma;
- Irradiation exposure;
- Drugs (used for chemotherapy; ketoconazole, spironolactone, cyproterone, synthetic anabolic steroids);
- Toxic substances (ethanol, marijuana, heroin, methadone, xenogenic estrogens, etc.);
- Autoimmune diseases;
- Systemic illness (liver failure, renal failure, severe malnutrition, anorexia nervosa, sickle cell disease, malignancies, amyloidosis, cystic fibrosis).

Male hypogonadism manifests by delayed puberty, if androgens hypoproduction starts during childhood; decreased secondary sexual characteristics, decreased libido and infertility or subfertility.

Pathophysiological basis for male hypogonadism treatment: (1) management of underlying disorder; (2) androgen replacement therapy.

Endocrine disorders of the ovaries

The ovaries are paired organs playing two important functions: steroidogenesis and gametogenesis. The ovaries produce estrogens (estrone, most biologically active estradiol, and estriol), androgens and progesterone.

Female reproductive organs have cyclic changes starting at menarche (first menstruation) until menopause (aging of reproductive system and stopping of menstruations). Female menstrual cycle is a classic example of infradian biological rhythms, lasting 20-36 days (28 days in average). Menstrual cycle has three phases: (1) follicular; (2) ovulation; (3) luteal. First day of the menstrual cycle is a first day of menstrual bleeding and a beginning of follicular phase. During this phase FSH production gradually rises; FSH stimulates growth of 6-12 follicles in the

ovary. Ovarian granulose cells produce estrogens in incremental quantity. LH concentration also begins to elevate, and LH stimulate ovarian theca cells to produce androgens, which are converted to estrogens by aromatase. One selected follicle, having highest aromatase activity and highest number of receptors to the LH, starts to grow faster. Other follicles undergo to atresia via induction of apoptosis of their cells.

Ovulation begins one day before LH surge and finishes one day after LH surge. According with positive (induced by high concentrations of estrogen, oxytocin and inhibin) feedback regulation, LH concentration elevates approximately to 6-10 times compared with preovulatory period. Such high level of LH stimulates plasminogen activation in the theca and granulose cells. Plasmin, relaxin and progesterone activate other metalloproteinases which degrade components of follicular matrix. Progesterone also stimulates local synthesis of vasodilators (prostaglandin E and hydroxyeicosatetranoic acids) and multiple biologically active paracrine acting substances (cytokines, bradykinin, ROS, RNS, Ang II, PAF, etc.). As a result of vasodilation and increased vascular permeability, blood serum transudates in the follicular cavity. Corresponding contraction of ovarian smooth muscle cells leads to pressure elevation inside the follicle, and degradation of the follicular wall result in its rupture and release of oocyte in the abdominal cavity. At the moment of ovulation, high concentrations of LH favor completing of the oocytes' reduction division with haploid number of chromosomes in the oocyte.

During next, luteal phase, LH stops division of cells of ovulated follicle, and ovulated follicle is transformed to the corpus luteum. Luteinization of granulose cells takes several hours; during this period activity of transcription factors is changed, intracellular signaling pathways are activated and cellular phenotype is changed dramatically. Luteal cells produce high amounts of progesterone and in smaller amounts – estrogens. Progesterone plays an essential role in the implantation of the fertilized oocyte in the endometrium. Theca cells synthetize androgens, which are converted to estrogens in granulose cells. If implantation has not occurring, LH synthesis decreases, and corpus luteum regresses and replaces with connective tissue. During this phase, estrogens and progesterone via negative feedback mechanisms suppress gonadotropins synthesis and secretion. Low FSH and LH are unable now to stimulate steroidogenesis; level of sex steroids decreases more due to corpus luteum regression. Such very low sex steroids concentrations will stimulate FSH and LH secretion, and menstrual cycle will repeat again. Dynamics of some changes during menstrual cycle is illustrated in the Fig. 7-14.

To better understand female endocrine disorders, it is important to summarize basic functions of female sex steroids. Due to wide distribution of estrogen receptors not only in cells of reproductive system, but in almost all cells, estrogens have many functions in female organism:

- Regulation of gonadotropins secretion;
- Development of secondary female sex characteristics (female-like body composition, social behavior, high voice, development of mammary glands,

female-type fat distribution);

- Changes during menstrual cycle: regulation of follicles growth and maturation, regulation of ovulation, vascularization of the vagina, stimulation of vaginal epithelial cells proliferation, maintenance of vaginal microbiota, stimulation of uterus vascularization and growth, regulation of cyclical endometrial changes, proliferation of breast milk ducts;
- Activation of blood coagulability via stimulation of I, V, VII and IX clotting factor synthesis;
- Remodeling of bone tissue, stimulation of bone formation and suppression of bone resorption;
- Activation of RAAS, sodium and water retention;
- Regulation of fat deposition, and regulation of lipoproteins metabolism;
- Regulation of the cardiovascular system activity;
- Stimulation of synthesis of globulin, binding cortisol, thyroid hormones and sex steroids;
- Regulation of CNS activity, control of sexual activity;
- Modulation immune system activity: regulation of T-cells differentiation and activity, control of leucopoiesis, regulation of WBCs' functional activity, modulation activity of APCs;
- Maintenance of skin integrity.

Progesterone also plays important roles. It regulates implantation of fertilized oocyte in the secretory transformed endometrium and suppresses myometrium contractility during this period. Progesterone also regulates timely gonadotropin secretion and participates in the ovulation. This hormone provides genome integrity in epithelial ovarian cells. Progesterone causes formation of a dense cervical mucus, which is poor permeable for spermatozoa and regulates proliferation of vaginal epithelial cells. In endometrial cells progesterone decreases their sensitivity to estrogens via down-regulation of estrogen receptors in these cells. It causes hypertrophy of mammary glands and stimulates growth of their lobules. Under influences of progesterone, basal (rectal) body temperature rises to 0.2-0.5^{o}C during luteal phase of menstrual cycle. It also stimulates fat accumulation and decrease muscular tone of the hollow organs. At high concentrations, progesterone stimulates Na^{+} excretion. Progesterone also stimulates respiration thus decreasing P_aCO_2 in the alveolar air during luteal phase of menstrual cycle. Progesterone and it metabolites produced locally in the CNS, regulate myelination of nerve endings, modify sexual female behavior, cognition, sleep, emotional reactions, etc. Cells of immune system have progesterone receptors; that is why it regulates functional activity of the immune system. For example, it polarizes immune response towards Th2 predomination, which is necessary for suppression of cellular-mediated maternal immunity during pregnancy and provides pregnancy prolongation.

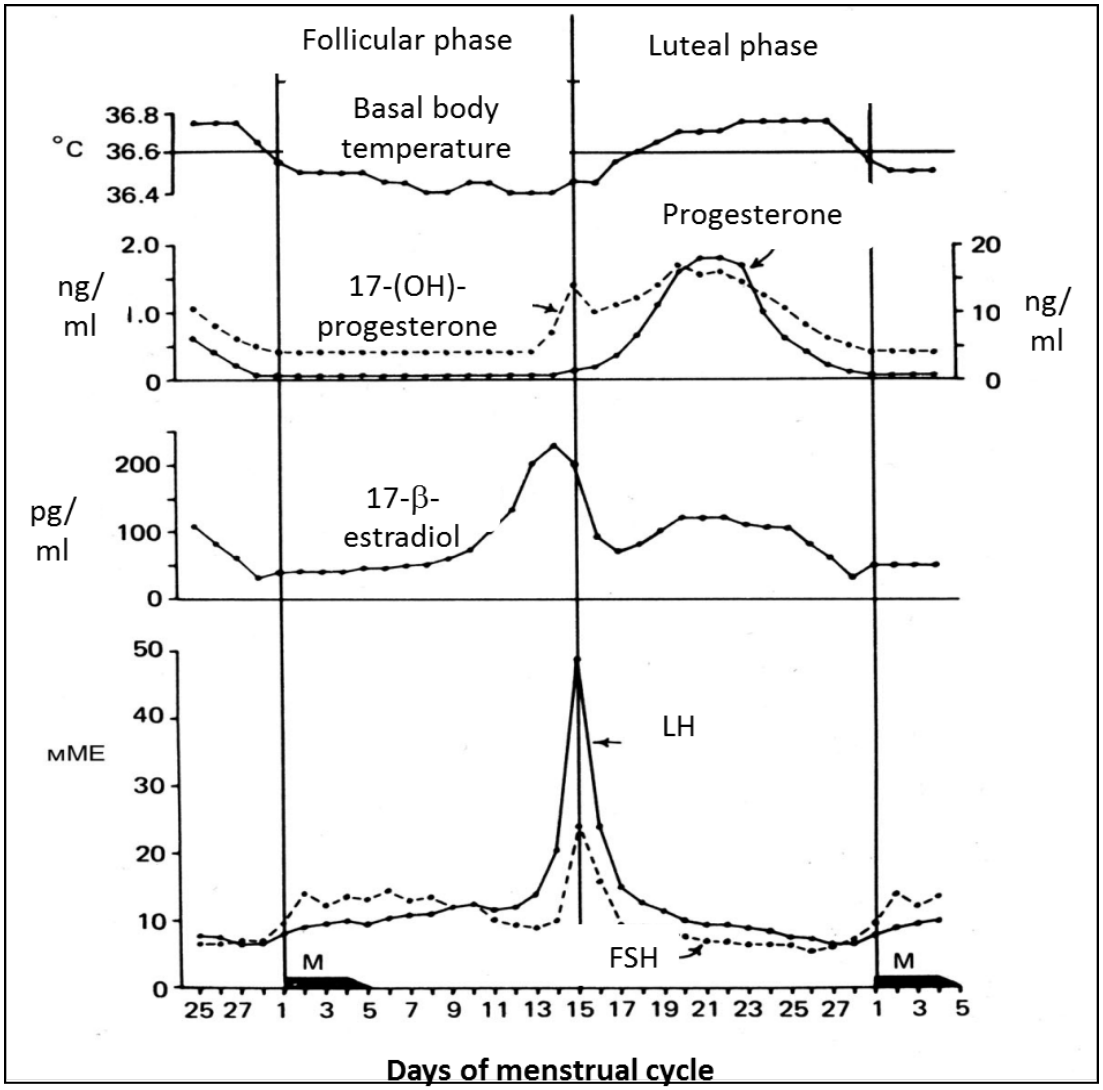


Figure 7-14. Physiology of menstrual cycle
(According with R.K. Murray, D.K. Granner, P.A. Mayes, V.W. Rodwell, 1993)

Androgens in females are produced in the adrenal cortex and in ovaries and participate in the regulation of different physiological functions. Firstly, they are substrate of aromatase reaction. Secondly, they regulate folliculogenesis. Thirdly, androgens control development of skeletal muscles. Next, adrenal androgens provide hair pubic and axillar growth. Androgens also control formation of bone tissue and stimulate closure of epiphyseal zones of bone growth, stimulate erythropoietin synthesis; regulate hair growth and activity of sebaceous glands. Androgens influence on the immune system activity: they increase T-regs count and decrease B-cells number. Some androgens (DHEA and DHEAS) prevent breast and endometrial cancer development. Androgens participate in sexual orientation development and regulate female sexual activity.

Female endocrine disorders can be classified into hypo- and hypergonadism; primary, secondary and tertiary; hereditary and acquired. Such disorders manifest

by different syndromes: delayed of precocious puberty, menstrual disorders, dysfunctional uterine bleeding, subfertility or infertility, spontaneous pregnancy losses, premature menopause and endocrine-related disorders of mammary glands. Most of these disorders are out of the view of the present textbook; they are described in specialized manuals for gynecologists and endocrinologists. Nevertheless, a short overview of some menstrual disorders will be presented below.

Menstrual cycle disorders

Basic characteristics of normal menstrual cycle are following: (1) duration of 21-36 days; (2) normal general state and painless menstruations; (3) volume of blood loss during one menstruation 30-80 ml, while up to 80% of blood loss occurs following first two days of menstruation; (4) duration of menstruation 3-7 days. Terminology describing menstrual disorders is presented in the Table 7-11.

Table 7-11. Terminology of menstrual cycle disorders

Terms		Definition
Hypomenstrual syndrome	Hypomenorrhea	Scanty and infrequent menstruations
	Oligomenorrhea	Shortening of period of menstrual bleeding
	Opsomenorrhea	Rare menstruations
Amenorrhea		Absence of menses in females at childbearing age following 3 months
Menorrhagia	Hypermenorrhea	Increased volume of menstrual blood loss
	Polymenorrhea	Increased duration of menstruations
	Proiomenorrhea	Shortened intervals between menstruations
Metrorrhagia		Acyclic uterine bleeding unrelated to menstruations
Algodismenorrhea (dismenorrhea)		Painful menstruations
Luteal phase insufficiency		Consequence of inadequate activity of the corpus luteum and progesterone deficiency leading to disorders of fertilized oocyte implantation and pregnancy development
Pathologic anovulation		Absence of ovulations in females at childbearing age on the assumption of pregnancy and lactation exclusion
Oligoovulation		Increased frequency of anovulatory menstrual cycles more than 10% of total menstrual cycles during year

The most severe menstrual disorder is amenorrhea. Amenorrhea can be classified into physiological (in girls before puberty, postmenopausal females, pregnant and lactating females) and pathological. Pathological amenorrhea may be true,

due to pathologic processes affecting any component of menstrual cycle regulation: brain cortex → hypothalamus → pituitary gland → ovaries → uterus and disorders of other endocrine glands, especially thyroid and adrenal glands or extragenital pathologies, or false, when cyclic changes in the ovaries and endometrium are normal, but menstruations are absent due to atresia of cervical duct, vagina, or hymen. Pathologic amenorrhea also is subdivided into primary and secondary; hyper- and hypogonadotropic. Primary amenorrhea is an absence of menstruations in girls older than 16 years. Secondary amenorrhea is a disappearance of menstruations, which were present earlier.

Primary amenorrhea is resulted from different disorders:

1. Abnormal cyclic secretion of GnRH in the hypothalamus and insensitivity of the pituitary gland cells to GnRH caused by genetic and acquired causes;
2. Disorders of secretion and/or action of gonadotropins;
3. Disorders of steroidogenesis in the ovaries or in the adrenals;
4. Androgen insensitivity syndrome;
5. Anatomical defects of external and/or in external genitalia.

Causes of secondary amenorrhea are summarized in the Table 7-12.

Table 7-12. Etiology of secondary amenorrhea

Forms of secondary amenorrhea		Causes of secondary amenorrhea
Hypothalamic amenorrhea	Functional	**Psychogenic amenorrhea:** repeated stress, fear of pregnancy, or, in contrast, compulsive craving of pregnancy
		Amenorrhea complicated disorders of feeding behavior and malnutrition: bulimia, anorexia nervosa, protein-deficiency diet, severe weight loss
		Amenorrhea due to extreme physical exercises (in females-athletes, gymnasts, ballet dancers, and in intensive training females)
	Organic	Tumors, especially craniopharyngioma; infiltrative diseases (sarcoidosis); vascular diseases; metabolic diseases (hemochromatosis); trauma; postradiation injury
Pituitary amenorrhea		**Hypopituitarism** (head trauma; tumors; postradiation injury; metabolic diseases (hemochromatosis); infiltrative diseases; pituitary apoplexy; damage of pituitary gland in tuberculosis, AIDS; postpartum hypopituitarism (Sheehan's syndrome);

	Hyperproduction of other pituitary hormones – GH, ACTH, and prolactin
Adrenal amenorrhea	**Hyperandrogenemia of adrenal origin** – defects of basic steroidogenic enzymes; **hormone-producing adrenal tumors**; **chronic adrenal insufficiency** (autoimmune, traumatic, irradiation injury of adrenals; thrombosis of adrenal blood vessels; damage of adrenal glands during tuberculosis, syphilis, AIDS, etc.) with secondary ACTH hyperproduction
Amenorrhea complicated thyroid gland diseases	Diseases and injury of thyroid gland with hypo- or hyperthyroidism
Ovarian amenorrhea	Syndrome of premature ovarian failure; syndrome of resistant ovaries, polycystic ovary syndrome, hormone-producing ovarian tumors, postovariectomy state
Uterine amenorrhea	Damage of endometrium in endometritis, intrauterine synechia (Asherman's syndrome), uterus extirpation or amputation

PART VIII. PATHOPHYSIOLOGY OF THE NERVOUS SYSTEM

General overview of the nervous system disorders pathophysiology

Because the nervous system of humans is highly-organized and even until present time not fully investigated, it is impossible to explain pathophysiology of all neurological and psychiatric disorders here; so only fundamental mechanisms of selected neurological diseases will be discussed in the present part.

Diseases of the nervous system may have different origin: they may be degenerative, inflammatory, tumors, infectious, autoimmune, and related to vascular disorders, metabolic errors, electrolyte abnormalities. They also may be inherited or acquired. At least 350 genes-candidates were proposed as primary causes of inherited neurologic diseases with different type of inheritance. Gene mutations may have monogenic or polygenic trait of inheritance. Monogenic diseases are relatively rare. Some monogenic disorders are familial Alzmeimer's disease due to mutations of the amyloid precursor protein; Parkinson's disease resulted from protein α-synuclein mutation and some others. However, most neurological disorders are multifactorial, meaning cooperation of genetic base, abnormal environmental factors and prenatal programming. The latter two groups of factors may lead to epigenetic changes, which induce stable and potentially inherited epigenetic "marks" such as chemical modifications of DNA, modifications of histones and action of non-coding RNAs. For instance, schizophrenia-like disorders have not only genetic causes, but strong epigenetic "marks". Gene-dosage effects were detected in some neurological disorders.

Some genetic mutations affect ion channels, whose main function is formation and propagation of action potentials. Such disorders were termed as channelopathies, which include some forms of ataxia, migraine, epilepsy, myotonia, several forms of deafness, and many others. Channelopathies may be due to gene mutations affecting ion channels or autoimmunity, when antibodies bind with channel proteins and impair their functions. However, different toxins and drugs interact with ion channels and impair different functions of nervous system.

Disorder of synaptic neurotransmission is also a meaningful pathogenetic mechanism of neurologic diseases. Classically, neurotransmitters are synthetized in the nerve terminals, then release in the synaptic cleft, bind with ionotropic or metabotropic receptors on the postsynaptic membrane and cause biological effects. Released neurotransmitters can be destroyed in the synaptic cleft by specific enzymes, by reuptake or diffusion away from the synaptic cleft. Disorders of synaptic neurotransmission will result in impaired cell-to-cell communications. Such situation is common in some neurologic diseases: myasthenia gravis, which is characterized by formation of antibodies against receptors to acetylcholine on the postsynaptic membrane; Parkinson's disease, whose clinical presentations are due to imbalance between dopamine and acetylcholine in the basal ganglia; some forms

of epilepsy due to γ-aminobutyric acid (GABA) deficiency.

Cell-to-cell communications between different neural cells may be impaired also as a result of abnormal gap junctions. Most common causes of these disorders are mutations of proteins connexins. For instance, mutations of connexins 26 and 31 result in autosomal-dominant progressive loss of hearing.

Abnormal formation of myelin, which surrounds axons, may be due to inherited mutations or autoimmunity may lead to different demyelinating diseases.

Some neurologic disorders are originated from deficiency of neurotrophic factors such as nerve growth factor, brain derived neurotrophic factor, and others. Neurotrophic factors are classified into three groups: neurotrophins, glial cell line-derived neurotrophic family of ligands (GFLs) and neurokines. Basic functions of neurotrophic factors as molecules with pleiotropic effects are modulation of neuron growth, differentiation, survival and repair. They also are involved in the mechanisms of memory and learning. Abnormal concentration and/or action of neurotrophic factors are involved in the pathogenesis of neurodegenerative diseases. Use of recombinant neurotrophic factors is a new promising method in different traumatic, ischemic and neurodegenerative diseases affecting central and peripheral nervous system.

Excessive death of cells in the nervous system due to necrosis, necroptosis (programmed necrosis), autophagy and apoptosis is an important pathogenetic mechanism of different neurologic disorders including ischemic brain injury, neurodegenerative disorders, autoimmune diseases, etc. Traditional universal molecular mechanisms (ATP deficiency, oxidative and nitrozative stress, accumulation of intracellular free calcium, damage of membrane, nucleus, proteins and DNA) are basic factors that provoke irreversible cell injury and death. In addition to these factors, excitotoxicity, or activation of receptors for N-methyl-D-aspartate (NMDA) or non-NMDA receptors by excitatory amino acids (for example, glutamate) with subsequent necrosis or apoptosis of neural cells, is an important mechanism of ischemic brain injury. Activation of above-mentioned receptors results in oxidative and nitrozative stress and accumulation of intracellular calcium with activation of calcium-dependent enzymes. These events produce ATP deficiency and damage of cellular macromolecules. Depending on degree of ATP deficiency, neurons die from apoptosis (in case of slightly decreased ATP production) or necrosis (in case of severe ATP deficiency). Apoptotic death and necrotic death may coexist. Normally autophagy may be protective, especially microautophagy, because it helps to degrade damaged proteins. Dysregulation of this process may result in neurodegeneration, for instance, during Huntington's disease, Alzheimer's disease and Parkinson's disease.

Endoplasmic reticulum stress seems to be significant pathogenetic mechanism of neurologic diseases including Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and multiple sclerosis. Accumulation of misfolded proteins can result from gene mutations, aggregation of modified proteins, inflammation, metabolic alterations, oxidative and nitrozative stress, etc. Accumulation

of misfolded proteins initiates unfolded protein response, which is characterized by decrease in rate of protein translation, activation of proteins folding and activation of protein degradation machinery. Severe or prolonged endoplasmic reticulum stress activates apoptotic cell death program. Moreover, endoplasmic reticulum stress in neural cells initiates neuroinflammation.

Neuroinflammation is a process of central nervous system cells and immune cells interaction. Neuroinflammation can be classified into “infectious” (caused by viruses, bacteria, prions, protozoa) or “sterile”. The latter is common in different neurologic diseases like neurodegenerative diseases, ischemic and hemorrhagic stroke, traumatic brain injury, epilepsy and some others. Main hallmarks of inflammation are activation of microglial cells (microgliosis) and/or astrocytes (astrogliosis), and damage of the blood-brain barrier with infiltration of the nervous tissue with immune cells. Microglial cells are macrophages of mesenchymal origin, which monitor the CNS for pathogens. Microglial cells have different PRRs, which are activated by PAMPs or DAMPs. After that, activated microglial cells polarize to M1 (classically activated, proinflammatory phenotype) or to M2 (alternatively activated, anti-inflammatory phenotype). M1 microglial cells produce sufficient amounts of ROS, RNS, proinflammatory cytokines and lack of neurotrophic factors thus mediating chronic inflammation in the CNS, damage of neurons and increase in the blood-brain barrier permeability. In turn, M2 microglial cells release anti-inflammatory cytokines, neurotrophic factors, and enzyme arginase, which degrading L-arginine, substrate for NO-synthase. Thus, M2 microglial cells mediate debris clearance, inflammation resolution and limit neuronal damage. Astrocytes are derived from ectoderm. They play different functions including metabolic support for neurons, regulating synapses, brain structure and repair. Activation of astrocytes during inflammation results in glial scar formation.

Disorders of mitochondrial homeostasis are also meaningful pathogenetic mechanism of neurologic diseases. Mitochondria are required for ATP synthesis, production of key metabolites, formation of ROS and RNS, regulation of intracellular calcium homeostasis, and programmed and non-programmed cell death. Mitochondria are also highly dynamic organelles that undergo fusion and fission. These processes are regulated by different dynamin-related GTPase proteins. In response to different physiological and pathological stimuli mitochondria are transported to intracellular sites with high bioenergetics requirements due to their movement along microtubules or actin filaments. Moreover, mitochondria can be transported between different cell types; for instance, neurons are able to release damaged mitochondria to astrocytes for their degradation and, in contrast, mitochondria move from astrocytes to neurons. Mitochondria also contain DNA (mtDNA), and mutations of mitochondrial DNA relate to different mitochondrial diseases affecting nervous system. The mitochondrial genome has approximately 15 times greater mutation rate than nuclear DNA due to high local production of ROS, lack of mtDNA repair mechanism and lack of protective proteins-histones in mitochondrial DNA. Some disorders caused by mutations in mtDNA and affecting

nervous system are numerous: some forms of seizures, ataxia, myoclonus, psychomotor retardation, psychomotor regression, hemiparesis and hemianopia, cortical blindness, migraine-like headaches, dystonia, and peripheral neuropathy. Decrease in number of mitochondria, disorders of mitochondria dynamics and mitochondrial dysfunction are key pathogenetic mechanisms of almost all neurodegenerative diseases.

Further to better understand the symptoms of neurologic disorders, specific terms describing them are listed in the Table 8-1.

Table 8-1. A short glossary of basic neurological terms

Term	Definition
Akinesia	(From Greek: a – negative+kinesis – movement); a lack of spontaneous movements
Anopsia	(From Greek: a – negative+opsis – vision); a defect of vision
Aphasia	(From Greek: a – negative+phasis – speech); a defect of the power of expression by speech or by comprehending spoken or written language
Apraxia	(From Greek: a – negative+pratto – to do); an inability to perform purposeful movements in the absence of paralysis
Asynergy	(From Greek: a – negative+syn – with+ergon - work); a disturbance of the proper association in the muscles contraction with improper sequence, or moment, or degree of movements leading to incorrect act
Ataxia	(From Greek: a – negative+taxis – order); a loss of power of muscle coordination with irregularity of muscle action
Athetosis	(From Greek: athetos – without position or place); a disorder of nervous system due to degenerative changes in the corpus striatum and cerebral cortex, which is characterized by bizarre, writhing movements predominantly of fingers and toes
Bradykinesia	(From Greek: brady – slow+kinesis – movement); an abnormal slowness of movements
Chorea	(From Greek: choros – a dance); a disorder characterized by irregular, spastic, involuntary movements of the limbs or facial muscles
Dementia	A chronic progressive syndrome, which is characterized by impaired cognitive capacity
Diplopia	(From Greek: diplous – double+ops – eye); a double vision
Dyskinesia	(From Greek: dys – disordered or difficult+kinesis – movement); an abnormality of motor function with involuntary, aimless movements
Dystonia	An involuntary muscle contractions leading to twisting movements or even abnormal posture

Hemiballism	(From Greek: hemi – half+ballismos – jumping); a forcible motor restlessness affecting one side of the body, which is resulted from injury of subthalamic nucleus
Hemiplegia	(From Greek: hemi – half+plege – stroke); paralysis of one side of the body
Nociceptive	(From Latin: noceo – to injure+capio – to take); a responsive to injurious stimuli
Nystagmus	(From Greek: nystagmos – a nodding); an involuntary oscillation of eyes
Paralysis	(From Greek: paralyein – to loosen, dissolve); a loss of voluntary action
Paraplegia	(From Greek: para – beside+plege – stroke); a paralysis of both extremities
Paresis	(From Greek: parienai – to relax); a partial paralysis
Ptosis	(From Greek: ptosis – falling); a drooping of the upper eyelid
Seizure	(From Latin: "sacire" – to take possession of) is a paroxysmal convulsive activity of muscles due to excessive hypersynchronous activity of neurons in the CNS
Tetraplegia	(From Greek: tetra – four+plege – stroke); a paralysis of both four extremities
Tics	A potentially suppressible brief stereotyped, repeated contractions of single or multiply groups of muscles
Tremor	A rhythmic oscillation of different body parts which

Disorders of sensitivity and pain

Simplified, neural pathways transmitting pain and temperature sensitivity can be illustrated as following: sensitivity fibers of peripheral nerves consisting from axons of 1st neurons in the intervertebral spinal ganglia→2nd neurons in the posterior horn → decussation of their axons on the opposite side of the spinal cord → tractus spinothalamicus → 3rd neurons in the thalamus → formation of the tractus thalamocorticalis → their axons terminate in the posterior central gyrus and the parietal lobe (Fig. 8-1).

Proprioceptive and tactile sensitivity pathway is following: sensitivity fibers of peripheral nerves consisting from axons of 1st neurons in the intervertebral spinal ganglia → posterior column of the spinal cord without any decussation → Goll's and Burdach's fascicles → 2nd neurons Goll's and Burdach's nuclei in the medulla oblongata → decussation of their axons in the medulla oblongata and formation of tractus bulbothalamicus → junction of this fibers with tractus spinothalamicus → lemniscus medialis in the medulla oblongata and in the pons → 3rd neurons in the thalamic lateral and medial nuclei → tractus thalamocorticalis → posterior central gyrus and the parietal lobe.

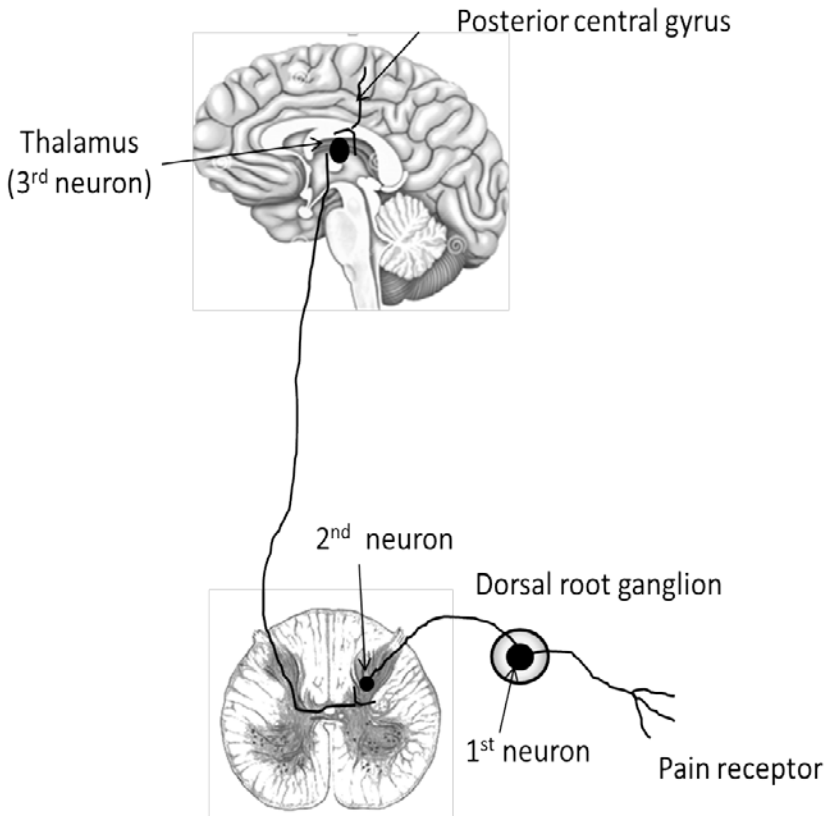


Figure 8-1. Schematic representation of the pain and temperature sensitivity neural pathway

Damage at any part of these pathways may lead to disorders of sensitivity:

- Anesthesia is a loss of any type of sensitivity. There are tactile, pain, temperature, stereognostic, proprioceptive anesthesia, topesthesia and total anesthesia.
- Hypoesthesia is a decrease in sensitivity.
- Hyperesthesia is an increase in sensitivity.
- Dysesthesia is a perverse sensitivity (for instance, a touch is recognized as a pain; cold is recognized as a heat, etc.).
- Synesthesia is a sensation of any irritation not only locally, at the site of action, but in any other region.
- Paresthesia is an abnormal sensation without any external stimuli (numbing sensation, sensation of "goose bumps crawling", sensation of twinge, etc.).
- Pain.

According with definition, which was proposed by International Association for the Study of Pain, **pain** is an unpleasant sensatory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. There are lots of classifications of pain:

I. Depending on its duration, pain can be classified into acute and chronic. Acute pain usually lasts less than 3 months; it also is considered to

be “physiologic”, or “good pain”, because of it has biological significance – to inform about any injury in the organism. Acute pain associates with clinical symptoms of SNS hyperactivation and a prominent emotional component. Chronic pain persists more than 3 months and is thought to be pathologic, or “bad pain”.

II. According with underlying cause, pain can be subdivided into nociceptive and neuropathic. Nociceptive pain appears after irritation of nociceptors (“nocere” from Latin means “to cause any harm”) by strong pressure, heat or cold, some chemical substances (most painful bradykinin, serotonin, prostaglandins, substance P, calcitonin gene-related peptide, H^+, K^+, acetylcholine, lactic acid, etc.). It is important to note, that prostaglandins do not excite nociceptors primarily, but enhance sensitivity of them. In turn, nociceptive pain is classified into somatic and visceral. Somatic pain starts after activation of nociceptors located in skin, connective tissue, bones and joints. As a rule, somatic pain is sharp, acute, and well localized. Visceral pain is a result of activation of nociceptors in the viscera. It is dull, aching, cramping and poor localized. Neuropathic pain is a result of any diseases of the nervous system (for example, diabetic neuropathy, toxic injury of peripheral nerves, or ischemia) and may be as acute as chronic. A good example of neuropathic pain is causalgia. Causalgia is a spontaneous burning pain, which occurs long after seeming trivial injury and manifests by hyperalgesia and allodynia. Hyperalgesia is an exaggerated response to noxious stimuli, whereas allodynia is a sensation of pain in response to innocuous stimuli.

III. Based on the nerve fibers involved in the pain impulses conduction, pain may be fast, sensing as a sharp, and slow, sensing as an unpleasant feeling. Fast pain is transmitted by Aδ pain fibers, whereas C pain fibers transmits slow pain.

IV. Pain may be local, occurring in damaged tissue or organ, referred and projected. For example, patients with myocardial infarction suffering not only from the local substernal pain, but also from pain in their left arms or shoulders, abdomen or neck (so-called Head’s zones). It is referred pain, which occurs because of afferents of affected nerves interact with other afferents in the same segment of the spinal cord. Projected pain developing after nerve stimulation. Thus, patient with contusion of the cubital articulation and resultant excitation of the ulnar nerve has pain in all upper extremity on the side of trauma according with area of excited nerve innervation. A variety of projected pain is a phantom pain, or pain in amputated extremity or its part. Phantom pain is a result of (1) damage of the thick myelin fibers, which are part of tactile and deep muscle and joint sensitivity, and (2) formation of neurynoma in the stump of the amputated extremity.

A pain control system (antinociceptive system) includes periaqueductal gray area with opioidoergic neurons, raphe magnus nucleus with serotoninergic neurons and pain inhibitory complex in the dorsal horns of the spinal cord with opioidoergic neurons. This knowledge is a base for pain treatment.

Pathophysiological basis for pain management (analgesia) include: (1) removal of the offending stimuli; (2) use of NSAIDs, which suppress COX activity thus diminishing prostaglandins synthesis and decreasing sensitization of nociceptors; (3) transection of peripheral nerves in some cases; (4) sympathicotomy in complex regional painful syndrome; (5) use of opioid-like drugs; (6) electrical stimulation of the posterior columns of the spinal cord; (7) transcutaneous electroneurostimulation of afferent fibers with large caliber; (8) stimulation of the nuclei in the brainstem; (9) drugs modifying serotoninergic or noradrenergic transmission (antidepressants).

Pain sensation disorders include hyperalgesia and hypoalgesia. Hyperalgesia is a hypersensitivity to pain, which is subdivided into primary and secondary. Primary hyperalgesia is an increased sensitivity of pain receptors to different nociceptive stimuli. Secondary hyperalgesia is resulted from facilitation of sensory transmission due to any lesion of the spinal cord and thalamus. Thalamic pain is usually splitting and obnoxious without exact localization; it is poorly correctable. Hypoalgesia is a hyposensitivity to the pain, which can be congenital (rare disorder) and acquired due to damage of the nociceptive system at any level. Hypoalgesia leads to loss of pain sensation of different noxious stimuli, and as a result, severe tissue or organ damage may occur.

Disorders of locomotor function

Locomotor function is regulated via hierarchical activity of the following parts of the CNS (Fig. 8-2).

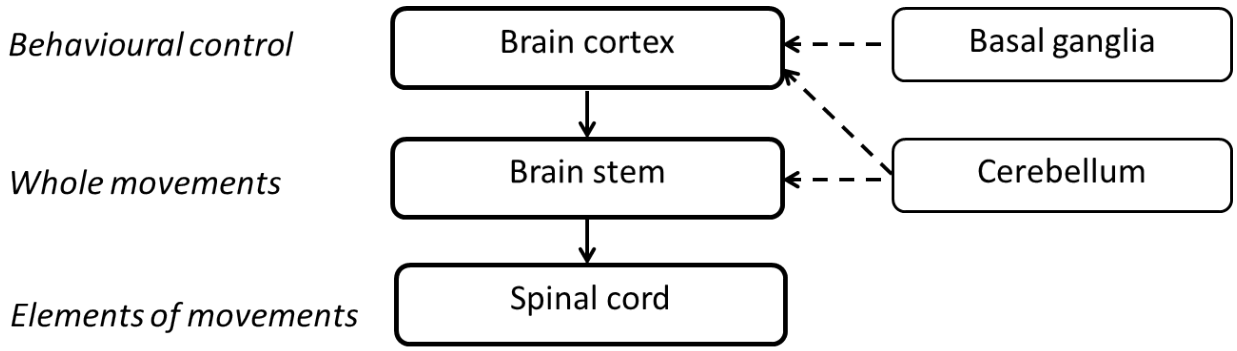


Figure 8-2. Regulation of locomotor function

Dashed lines indicate modulating effects

Central or 1st neurons of locomotor tract locate in the brain cortex (large pyramidal Betz' cells). Their axons connect brain cortex with 2nd motor neurons in the anterior horns of the spinal cord (tractus corticospinalis) and in the brain stem. Fibers from the 1st neurons also connect brain cortex with nuclei of the cerebral nerves via tractus corticobulbaris. Neural fibers from 2nd motor neurons pass to

skeletal muscles.

Disorders of locomotor function manifest by positive symptoms (pathologic reflexes, deblocking symptoms) or by negative symptoms (loss of movements and motor skills). Some of them are paralysis and paresis.

Paralysis is a complete loss of voluntary movements, whereas paresis is a decrease in strength and/or amplitude of voluntary movements. Depending on their localization, paralysis or paresis may affect single extremity (monoplegia or monoparesis, accordingly), half of a body (hemiplegia or hemiparesis), symmetrical extremities (paraplegia or paraparesis), and all extremities (tetraplegia or tetraparesis). Based on the site of damage of the locomotor tract, paralysis can be classified into central and peripheral (Table 8-2).

Table 8-2. Central paralysis vs. peripheral paralysis: comparative characteristic

Criteria	Central paralysis	Peripheral paralysis
Site of damage of locomotor tract	Central motor neuron in any part	Peripheral motor neuron in any part
Zone of affected muscles	Diffuse, affecting all extremity or even half of the body due to localization of motor neurons and their fibers in the close proximity	May affect separate groups of muscles or even muscular fascicles
Tone of affected skeletal muscles	Enhanced (Spastic paralysis) due to disinhibition of spinal cord activity	Decreased (Flabby, atonic paralysis), which is resulted from loss of contractile tone
Atrophy of affected muscles	Uncommon	Common, due to loss of neurotrophic impulses from the anterior horns of the spinal cord
Tendinous reflexes	Enhanced	Decreased
Pathologic reflexes	Common (Babinski's reflex, Rossolimo's digital reflex, Bechterew's reflex)	Uncommon
Presence of synkinesia (conjugate movements)	Common	Uncommon
Reaction of degeneration of affected nerve	Uncommon	Common

Hyperkinesia is an involuntary increased muscular movement (tremor, cho-

rea, atetosis, dystonia, myoclonus tics and seizures). Hyperkinetic disorders are hallmarks of the basal ganglia disorder; however, these disorders also may lead to hypokinetic syndrome. The basal ganglia are a group of interrelated subcortical structures (the caudate nucleus and putamen, which is termed as "striatum", the globus pallidus, substantia nigra and subthalamic ganglia).

Tremor is a rhythmic oscillation of different body parts which is resulted from intermittent contractions of skeletal muscles. It may be essential or related with Parkinson's disease, use of some drugs, neurodegenerative diseases, metabolic disorders, multiple sclerosis and psychogenic disorders.

Dystonia is an involuntary muscle contractions leading to twisting movements or even abnormal posture due to damage of the globus pallidus and thalamus. It may affect one or several groups of muscles. Dystonia may be primary (idiopathic, autosomal dominant, childhood-onset) or secondary (drug-induced or related to damage of striatum, pallidum, thalamus, cortex and brainstem).

Chorea is a rapid, dance-like patternless involuntary movement, which affect both distal and proximal groups of muscles, which is resulted from damage of the striatum. Chorea is a hallmark of the Huntington's disease – progressive fatal neurodegenerative disorder that associates with motor, cognitive and behavioral disturbances. The disease is characterized not only by chorea, but also dysarthria, gait disorders and oculomotor symptoms. Morphologically Huntington's disease is manifested by atrophy of the nucleus caudatus. Other causes of chorea include rheumatic fever caused by *Streptococcus hemolyticus group A* infection (Sydenham's chorea or Saint Vitus' dance), neuroacanthocytosis (related to hereditary hemolytic anemia – acanthocytosis), vascular and metabolic diseases, systemic lupus erythematosus and some other autoimmune disorders, hyperthyroidism and exposure to some drugs or chemicals (cocaine, lithium, CNS stimulating agents, anticonvulsants, and estrogens).

Athetosis represents continuous, wormlike twisting motions of the joints of any limb or even whole body due to lesions of the striatum and pallidum of any etiology.

Ballismus is a violent, impetuous, rushing motion of the limbs usually on one side of the body (hemiballismus). Ballismus reflects lesions of the subthalamic nuclei of any etiology.

Tics represent potentially suppressible, brief, stereotyped and repeated contractions of single or multiply groups of muscles. Tics may be sensory, motor or vocal. The latter manifest by grunting or repeating different words – echolalia (pronounced by other individuals), palilalia (own patient's words) or coprolalia (obscene words). Tics may be seen in patients with Tourette syndrome, a neurobehavioural genetic disorder that, besides tics, associates with attention-deficit hyperactivity disorder and vocalizations; some neurodegenerative disorders such as Parkinson's disease and Huntington's disease, after toxins or drugs (levodopa, neuroleptics) exposure, associated with trauma and psychogenic disorders. Myoclonus is sudden, short-term, arrhythmic, severe muscles cramps due to injury in cortical,

subcortical or spinal cord areas caused by hypoxia, metabolic disorders, toxins or drugs exposure or as a result of neurodegeneration.

Seizures are paroxysmal convulsive activity of muscles due to excessive hypersynchronous activity of neurons in the CNS. Seizures may be partial, when seizure activity in discrete brain regions is documented, and generalized, when diffuse brain regions are involved in the pathological activity. Seizures are hallmark of epilepsy, a neuropsychiatric multifactorial disease, or associated with other causes: trauma, hypoxic injury, hyperthermia, infections, and tumors affecting brain, cerebrovascular diseases, metabolic causes (hypo- or hyperglycemia, uremia, liver failure, electrolyte disorders, some endocrine disorders and some drugs exposure).

Ataxia is incoordination or clumsiness of movement that is not related to muscular weakness. Ataxia affects eye movement, speech with dysarthria, limbs, the trunk, stance or gait. Ataxia is classified into:

- Vestibular;
- Cerebellar;
- Sensory (proprioceptive).

Vestibular ataxia results from the central or peripheral injury in vestibular pathways (vestibular nerves, brainstem, cerebellar labyrinth of the inner ear, VIII nerve). This ataxia coexists with nystagmus and appears not in the horizontal position, but when a patient attempts to stand or walk.

Cerebellar ataxia is due to any lesions of the cerebellum or its connections with other brain structures. Clinical features of the cerebellar ataxia include irregularities in the rate, rhythm, amplitude and force of voluntary movements. Often it associates with muscular hypotonia and ocular abnormalities.

Sensory or proprioceptive ataxia is caused by disorders at any part of the proprioceptive pathways in peripheral sensory nerves, sensory roots, and posterior columns of the spinal cord or medial lemniscus. Sensory ataxia affects the gait and legs, movements and vibratory sense. Vertigo, nystagmus and dysarthria are absent.

Disorders of the spinal cord

Diseases of the spinal cord are often overwhelming and manifest by quadriplegia, paraplegia and disorders of sensation. Some of these disorders may be potentially reversible; but some progress gradually even during adequate treatment. Diseases which affect spinal cord are discussed in specialized neurological manuals, only traumatic spinal cord disorder will be highlighted below.

Hemisection of the spinal cord results in the **Brown-Sequard syndrome**. Pathological signs are detected caudal to the hemisected region. They include:

1. Loss of the position sense, tactile discrimination and vibration sense on the site of lesion due to interruption of the dorsal and dorsolateral funiculi.

2. Anesthesia for pain and temperature on the opposite side, because of damage of the tractus spinothalamicus (See Fig. 8-1).
3. Hemiplegia if lesion is in the upper cervical cord or monoplegia of leg if lesion is in the thoracic cord.

Disorders affecting brain structure and functions
Cerebrovascular diseases

Brain receives approximately 14% of the cardiac output at rest, and normal brain activities such as thinking or sleeping don't alter total cerebral blood flow. Cerebral blood flow (CBF) usually is 50 ml/min/100 g of brain tissue. In the absence of this normal blood flow, the brain has limited energy stores for normal functions. As a result, rapid fall of the CBF to zero will lead to death of brain neurons within 4-10 min., whereas decrease in CBF to 16-18 ml/min/100 g will result in brain infarction following 1 hour. Cerebral arteries have a good ability to autoregulation; cerebral blood flow is relatively constant at the range of mean arterial pressure 50-150 mm Hg. Stable poor treated arterial hypertension produces shift of this interval to upper values. That is why aggressive hypotensive therapy in hypertensive emergencies may lead to profound brain hypoperfusion, global cerebral ischemia and injury. Cerebral arteries are sensitive to p_aCO_2 fluctuations: hypercapnia results in a dilation of cerebral arteries and hypocapnia acts in opposite manner. Normally reliable blood-brain barrier protects brain from fluctuations of blood composition. The blood-brain barrier may be altered during different pathological conditions with secondary brain damage.

Cerebrovascular diseases may be acute or chronic. Pathophysiological classification of cerebrovascular diseases is illustrated in the Fig. 8-3.

Cerebrovascular diseases may be resulted from injury of large cerebral vessels or small, producing lacunar brain injury. Most common kind of cerebrovascular disease is a **stroke**. According to the clinical point of view, stroke, or cerebrovascular accident, manifests by abrupt onset of neurological deficit due to focal vascular cause. Pathophysiologically, stroke is characterized by irreversible damage of brain tissue. If quickly restoration of cerebral blood flow solves neurologic deficiency, disorder of cerebral blood flow with reversible damage of neurons seems to be transient ischemic attack (TIA). Today stroke remains a significant problem worldwide. Since 1990 until present time the absolute count of patients affected by this disorder increased significantly. Stroke affects 17 million people in the world each year; it is the second highest cause of death worldwide. The highest prevalence of stroke was detected in developed countries, whereas lower prevalence – in developing countries. These data indicate significant role of incorrect lifestyle in the pathogenesis of stroke and related pathologies.

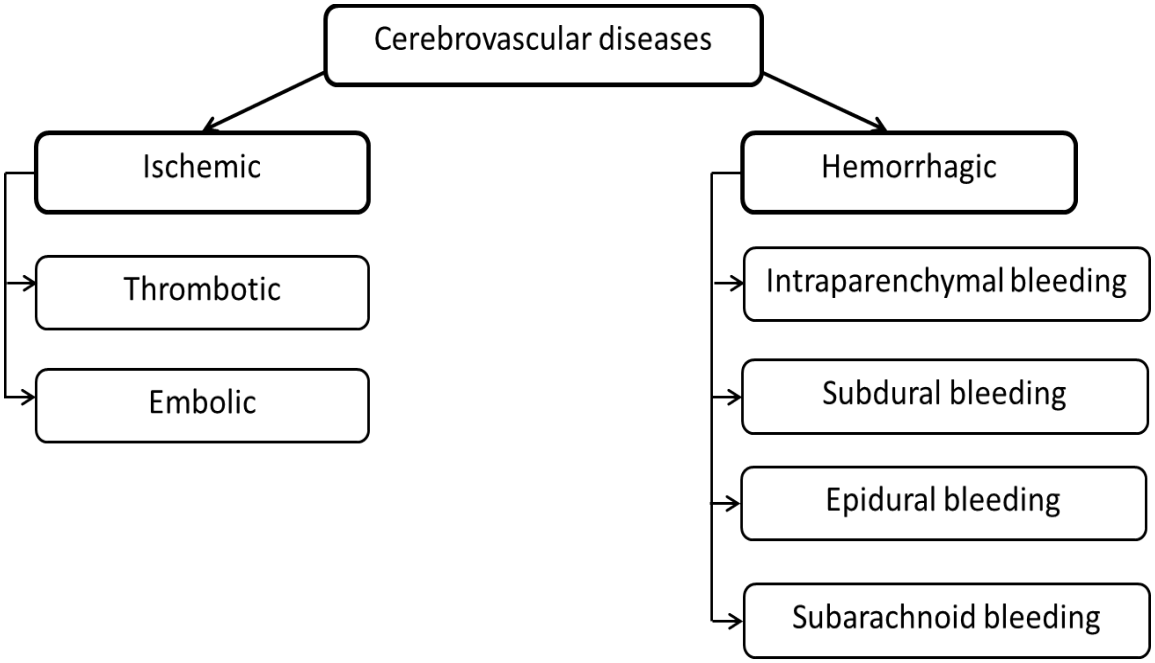


Figure 8-3. Classification of cerebrovascular diseases

The most common type of **stroke** is **ischemic**, reaching up to 85% among all types of stroke. Thrombosis of cerebral arteries usually complicates atherosclerotic arterial lesions or strongly associates with other components of Virchow's triad. Embolic occlusion of cerebral arteries may be resulted from embolism originated from different regions:

- Artery-to-artery embolism (emboli from carotid bifurcation, aortic arch or after arterial dissection);
- Cardioembolic embolism (risk of the embolism is high in atrial fibrillation, formation of mural thrombi in cardiomyopathies and after myocardial infarction);
- Embolism associated with valvular vegetations (mitral stenosis, prosthetic mitral valve, bacterial endocarditis);
- Paradoxical embolism (atrial septal defects, patent foramen ovale, atrial septal aneurysm).

Abrupt impairment of cerebral blood flow produces the net of pathologic events illustrated in the Fig. 8-4. As a result, site of brain injury, consisting of an ischemic core zone with neurons, dead mostly due to necrosis and to a lesser extent – from apoptosis, and ischemic penumbra zone with reversibly damaged neurons, which will transit to brain infarction, is formed (Fig. 8-5).

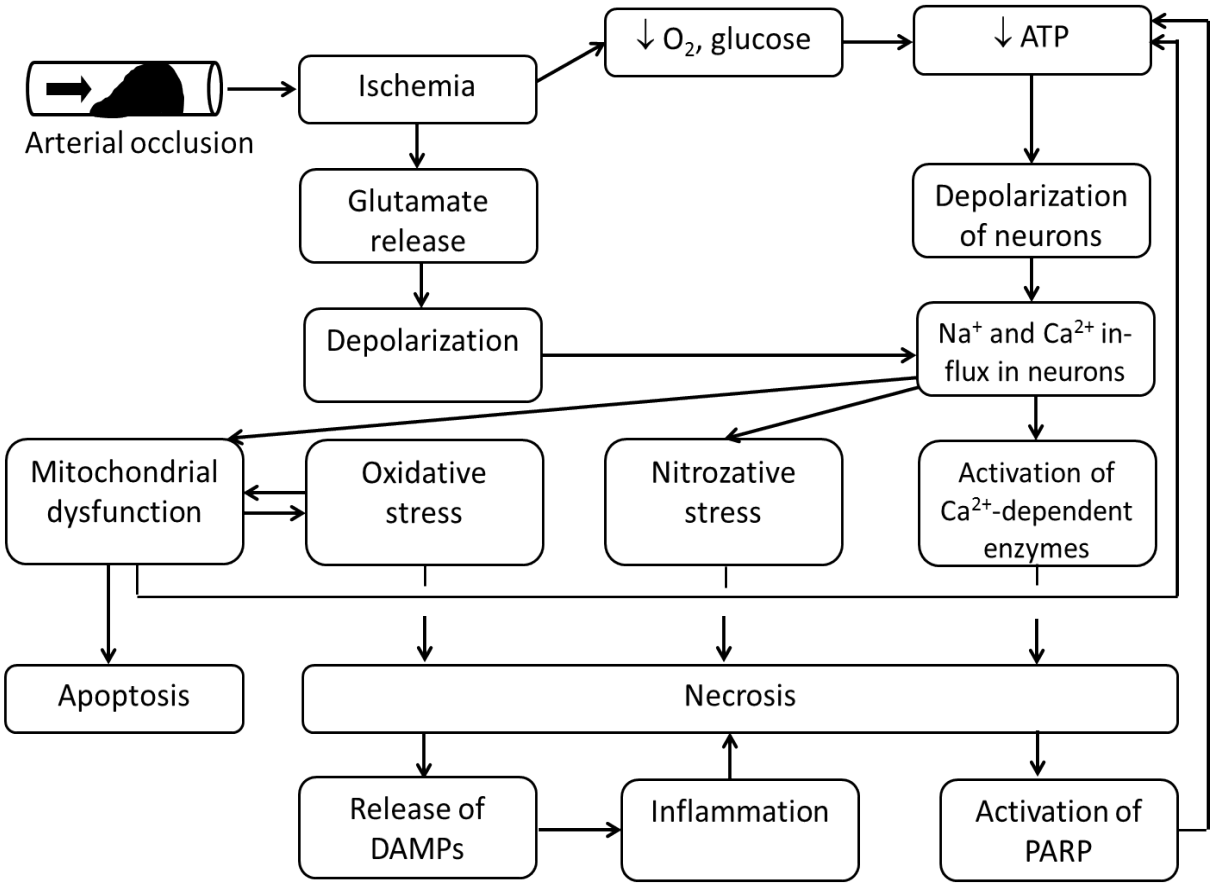


Figure 8-4. Pathogenesis of ischemic stroke during acute phase

DAMPs, Damage Associated Molecular Patterns; PARP, Poly-A ribose polymerase

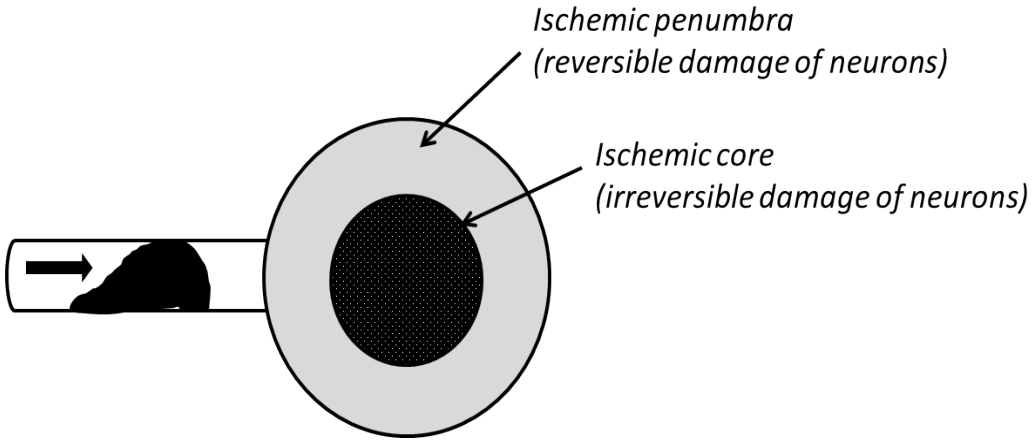


Figure 8-5. Zones of ischemic brain injury

One of the important goals of stroke management is a prevention of ischemic penumbra expansion.

Abrupt impairment of cerebral blood flow results in neuronal oxygen and glucose deprivation, which produce ATP deficiency with subsequent neurons de-

polarization and swelling. Influx of Ca^{2+} in neurons results in two basic adverse events: (1) activation of all calcium-dependent enzymes like as ATPases, phospholipases, proteinases and endonucleases causing injury of neurons; and (2) release of glutamate from synaptic cleft with subsequent activation of postsynaptic glutamate receptors and augmentation of calcium flux in damaged neurons (so-called "excitotoxicity"). Lack of oxygen and accumulation of intracellular calcium are main causes of mitochondrial dysfunction, which is characterized by ROS accumulation and releasing of apoptosis-inducing substances. Oxidative and nitrozative stress (the latter is initiated by inducible NO-synthase activation) cause damage of proteins, membrane lipids and nucleic acids in neurons. In response to DNA damage its repair is initiated via activation of ATP-dependent poly-A ribose polymerase (PARP). As a result, more severe ATP deficiency occurs. Irreversible damage of neurons and their death from necrosis results in DAMPs release, which trigger "sterile" neuroinflammation with activation of neurons and glial cells with secondary injury of brain cells. Untimely restoration of impaired cerebral blood flow (untimely reperfusion) often leads to reperfusion injury and expansion of ischemic core and ischemic penumbra zone via oxidative and nitrozative stress, accumulation of intracellular calcium and stimulation of neuroinflammation.

Clinical picture of ischemic stroke depends on localization of vascular event and injury of neurons in specific brain areas (Table 8-3):

Table 8-3. Clinical features of ischemic stroke in different vascular beds of the brain

Cerebral artery	Area of brain vascularization	Basic neurologic symptoms
Middle cerebral artery	Lateral parts of the frontal, parietal, occipital and temporal cortex with adjacent white matter; caudate, putamen, internal capsule	Contralateral hemiparesis, sensory loss, aphasia, spatial desorientation
Internal carotid artery	A part of the circle of Willis; divides into the middle and anterior cerebral arteries	Ipsilateral blindness, signs of middle cerebral artery obstruction
Anterior cerebral artery	Medial areas of the frontal and parietal cortex, anterior part of the corpus callosum	Contralateral hemiparesis, sensory loss
Posterior cerebral artery	Distal segments: medial occipital and temporal cortex with underlying white matter, posterior part of the corpus callosum Proximal segments: upper midbrain, thalamus	Contralateral hemianopia, memory impairment
Basilar artery	Lower midbrain, pons, upper and mid cerebellum	Contralateral hemiparesis, sensory loss, bulbar or cere-

		bellar signs
Vertebral artery (posterior inferior cerebellar artery)	Medulla, low cerebellum	Loss of facial sensation, ataxia, contralateral hemiparesis, sensory loss
Superior cerebellar artery	Cortex, medullary center and the central nuclei of the cerebellum, pons, superior cerebellar peduncle and inferior colliculus of the midbrain	Ataxia, headache, nausea, dysarthria, somnolence, contralateral hemiparesis

After stroke, early poststroke phase is initiated, which is characterized by starting of resolution response. Neuronal repair occurs in brain regions connected to injured area. The reorganization of connections within the affected brain is termed as plasticity. Basic processes of such spontaneous biological recovery include:

- Axonal sprouting, which associates with good poststroke outcomes;
- Dendritic branching;
- Synaptogenesis;
- Neurogenesis;
- Gliogenesis.

Process of repair is initiated by genetic and, especially, epigenetic changes leading to brain plasticity via expression of different neurotrophic factors, especially BDNF (Brain Derived Neurotrophic Factor).

Pathophysiological basis for ischemic stroke management: (1) supporting of vital functions; (2) thrombolysis as soon as possible (optimal efficacy of thrombolysis with tissue plasminogen activator was shown if patients were treated following 4.5 hours after the onset of stroke; (3) endovascular techniques (endovascular mechanical thrombectomy); (4) antithrombotic therapy (antiplatelet drugs, anticoagulants); (5) neuroprotection (for instance, hypothermia in patients with cardiac arrest); rehabilitation after stroke.

Results of translational researches now implicate preclinical studies to improve stroke treatment. Some new approaches were proposed to stimulate neuronal growth: purine nucleotide inosine, which initiates axonal growth and sprouting; Growth and Differentiating Factor 10 (GDF10), which promotes axonal sprouting; endogenous or exogenous stem cells, which stimulate trophic factors and modulators of inflammatory pathways in affected brain. A promising approach is thought to be blocking inhibitors of neuronal growth. For instance, myelin-associated proteins block neuronal regeneration. Antibodies against these proteins (anti-NogoA antibody) stimulate axonal growth. Some chondroitin sulfate proteins also inhibit axonal growth. The enzyme chondroitinase ABC degrades chondroitin sulfate thus

potentiating biological recovery of the affected brain. Inhibitors of some molecules (semaphorins, ephrin-5) that inhibit axonal growth cone were proposed as novel agents improving stroke outcomes. Different epigenetic modulators now are at a scope of investigation.

Hemorrhagic stroke accounts for approximately 15% among all types of stroke. Hemorrhagic stroke is classified into diffuse and local. Diffuse hemorrhagic stroke is characterized by bleeding into the subarachnoid space (most commonly) due to rupture of aneurysms affecting cerebral arteries or intraventricular space. Local hemorrhagic stroke means intraparenchymal (intracerebral) hemorrhage, which usually complicates hypertensive vascular disease or different vascular malformations. Rupture of any cerebral vessel occurs often in individuals having definite risk factors: arterial hypertension, smoking, binge drinking, using of sympathomimetics, anticoagulants or thrombolytic agents, amyloid angiopathy, leukemia, polycythemia vera, thrombocytopenia, hemophilia, and vasculitis. It is important to note, that mortality rate of intracerebral hemorrhages reaches to 40% within 1 month after event. Pathogenesis of intracerebral hemorrhage is represented in the Fig. 8-6.

Hematoma produces mass effect compressing brain tissue. Such compression results in perihematomal ischemia and related primary injury of brain cells. Neurons are most susceptible to injury than glial cells. From first day after intracerebral bleeding macrophages begin to degrade erythrocytes inside hematoma with releasing of hemoglobin from destructed red blood cells. Hemoglobin further is degraded to globin and heme; heme is converted subsequently or into met-Hb or into biliverdin, which is metabolized by hemoxygenase into carbon monoxide (CO) and free iron. These products were recognized as toxic blood-derived products due their pathologic effects. For example, met-Hb results in stimulation of heme release, protein carboxylation, oxidation of LDL and brain injury. Free hemoglobin and free iron promotes oxidative stress with irreversible damage of neurons. Heme itself stimulates inflammatory response in the brain via direct activation of the TLR4. Inflammation is potentiated by DAMPS releasing from irreversibly damaged brain cells. Free iron stimulates glutamate release from nerve endings with glutamate excitotoxicity, which damages neurons. Free iron also decreases nitric oxide bioavailability resulting in angiospastic brain ischemia. Excessive iron impairs redox state of neurons, promotes oxidative stress and impairs DNA repair response. Intracerebral bleeding also activates clotting system with local hyperproduction of thrombin. Thrombin per se activates protease-activated receptors (PARs) thus leading to inflammation in the brain tissue, and disrupts blood-brain barrier provoking edema formation. The net of these reactions integrates secondary injury of brain cells following intracerebral hemorrhage. Brain cells dying from necrosis, necroptosis (programmed necrosis), apoptosis, and autophagy.

Intracerebral hemorrhage stimulates different endogenous defensive mechanism such as expression of iron-handling proteins (haptoglobin and hemopexin), activation of microglial macrophages and astrocytes. Polarization of macrophages

from M1 to M2, synthesis of proresolving cytokines and chemokines, angiogenic and neurotrophic factors (HIF-1, erythropoietin, VEGF, angiopoietins-1 and 2, thrombin, others) are parts of inflammation resolution. Following several months after stroke collapsed cavity with hemosiderin-loaded macrophages is detected.

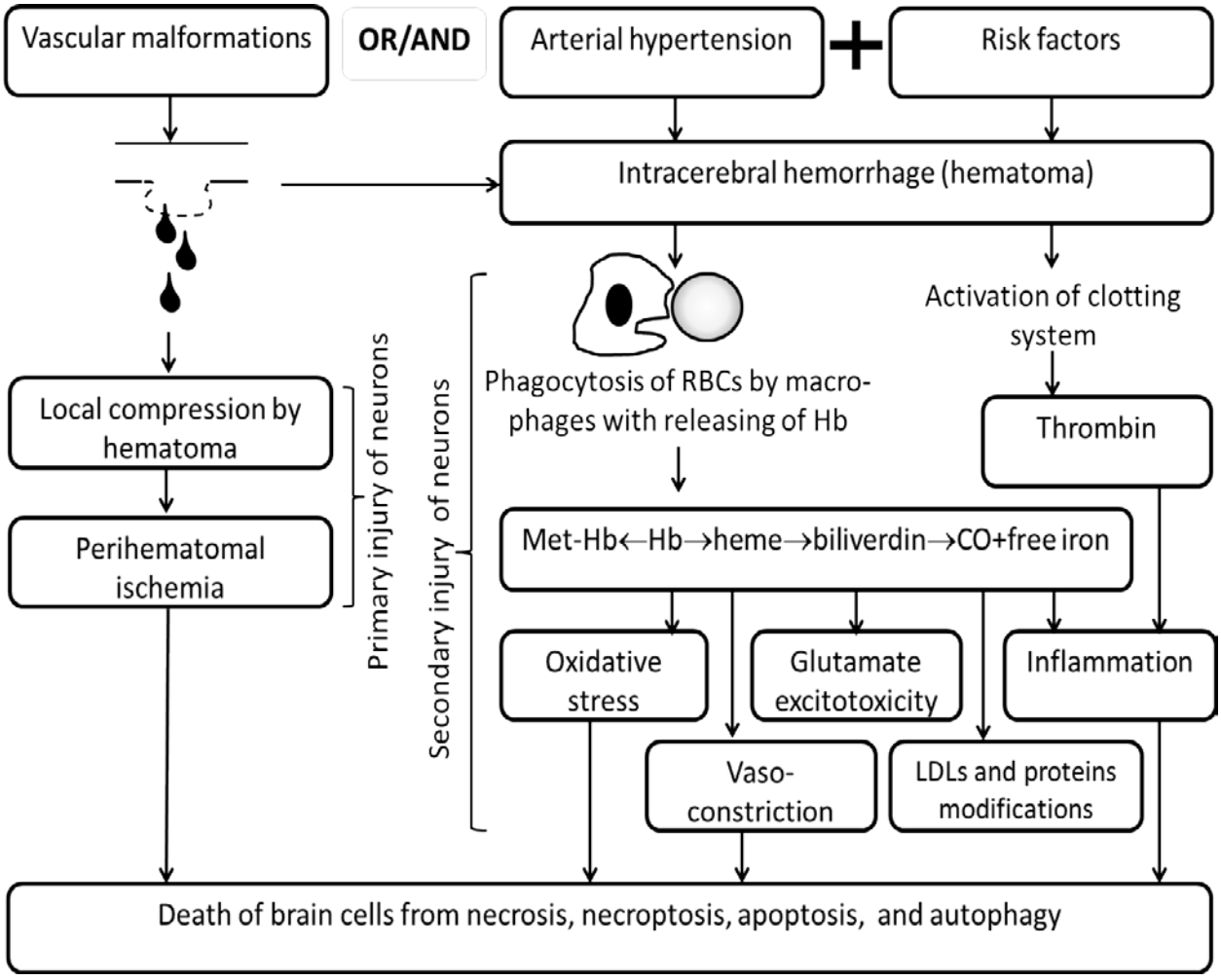


Figure 8-6. Pathogenesis of intracerebral hemorrhage

Pathophysiological basis for intracerebral hemorrhage management: (1) supporting of vital functions and management of blood pressure to prevent hematoma expansion; (2) recombinant VII factor, fresh-frozen plasma and platelets in thrombocytopenia within 4 hours after onset of hemorrhage; (3) surgical therapy to evacuate blood clot.

Neurodegenerative diseases

Common hallmarks of neurodegenerative diseases include progressive neuronal loss in specific brain regions and different intracellular inclusions containing

protein aggregates. Clinical picture of these diseases vary from dementia (in Alzheimer's disease), movement disorders with hypokinesia (Parkinson's disease), hyperkinesia and motor neuron disease. Selected neurodegenerative diseases will be discussed further.

Alzheimer's disease

Alzheimer's disease (AD) is a multifactorial progressive neurodegenerative disease causing dementia in elderly, which is characterized by memory loss, difficulties in solving problems and disorientation in time and space. Firstly the disease was described by German psychiatrist Alois Alzheimer in 1907. At 2006, more than 24 million individuals were affected worldwide, and progressive growth of AD incidence is registered now. AD is not only a medical, but also a social problem with high cost.

The disease is classified into most common sporadic and relatively rare familial form. According with a clinical point of view, AD affects individuals after 60-65 years old (so-called "late AD") or before 60-65 years old ("early AD"). Early form of the disease is diagnosed only in 1-6% of all patients suffering from AD. Both forms have strong genetic predisposition, but most role of abnormal genes play in early AD with autosomal dominant trait of inheritance. Three most common mutated genes – APP, PSEN1 and PSEN2 are involved in the development of early AD. APP gene is located on chromosome 21 and encodes amyloid precursor protein, whose abnormal proteolytic degradation results in the accumulation of β-amyloid and neurodegeneration. Patients with Down's syndrome (21 chromosome trisomy) have a greater chance for AD development. PSEN1 (presynilin 1) gene is located on chromosome 14 and encodes protein that forms catalytic site of γ-secretase complex, an enzymatic complex degrading amyloid precursor protein. PSEN2 (presenylin 2) gene is located on chromosome 1 and also encodes a component of γ-secretase complex. Most common mutated gene in sporadic form of AF is APOE located on chromosome 19, encoding similar apolipoprotein. Apo E polymorphism associates with greater risk of AD via stimulation of β-amyloid aggregation and protein τ hyperphosphorylation. Documented risk factors of AD include vascular causes which accelerate atherosclerosis (dyslipidemia, smoking, arterial hypertension, etc.), metabolic causes (obesity, diabetes mellitus) and psychosocial factors (low educational status, lack of social interactions, etc.).

Morphological hallmarks of AD are following: β-amyloid peptide aggregates in the extracellular space and intracellular inclusions of neurofibrillary tangles rich in microtubules-associated protein τ (tau) and neuritic plaques, and increased neuroinflammation. Different cells can be affected during AD: neurons in locus ceruleus, the nuclei of the brain stem, reticular formation, amygdala, substantia nigra, striatum, hypothalamus, thalamus, claustrum, and selected regions of brain cortex. Glial cells and blood vessels' cells also are affected. Loss of neural cells results in brain atrophy. At least 80% of neurons in the hippocampus, which is responsible for memory formation, die before cognitive impairment seen in pa-

tient. After diagnosis, average survival is approximately 7 years. At the present time, no any effective disease-modifying management is available in the clinical practice. To understand new translational approaches for AD treatment, it is necessary to understand mechanisms of the disease development.

Several molecular mechanisms were proposed for AD pathogenesis:

1. Alterations in cholinergic transmission due to impairment of choline intake, abnormal acetylcholine in the synaptic cleft, deficiency of nicotinic and muscarinic receptors, dysfunctional production and action of neurotrophins, abnormal axonal transport of acetylcholine and death of cholinergic neurons. This theory was historically proposed firstly, but now cholinergic mechanisms are thought to be not cause, but consequences in AD. Abnormal cholinergic signaling strongly relates to hyperactivation of NMDA receptors with subsequent excessive depolarization of postsynaptic membrane, accumulation of intracellular Ca^{2+}, mitochondrial ROS hyperproduction, activation of NO-synthases, neuronal damage, apoptosis and extracellular deposition of filaments similar to neurofibrillary tangles. Different groups of drugs act on these pathogenetic mechanisms: acetylcholinesterase inhibitors, cholinergic precursors, allosteric cholinergic receptors activators, and NMDA receptors antagonists.
2. Accumulation of β-amyloid. It occurs over a long period of time, usually more than 10 years before symptoms appearance. The protein β-amyloid consists from 37-43 amino acids and has several isoforms with different solubility. This protein is formed from the precursor – amyloid precursor protein (APP) consisting from 695-770 amino acids. The APP is a transmembrane glycoprotein with unclear functions, which is expressed during cellular stress. The APP is processed by proteolytic enzymes – β and γ-secretases with releasing of peptides with different properties and functions. In patients with AD γ-secretase releases hydrophobic β-amyloid consisting from 42 amino acids, which after secretion aggregates and accumulates in the extracellular plaques. Further fate of this protein is depending on the rate of its generation and clearance. β-amyloid is able to pass through the blood-brain barrier with exosomes and release in the blood via lipoprotein receptor-related protein 1 (LRP-1). It was documented, that number of LRP-1 reduces with age thus predisposing to β-amyloid accumulation. In turn, opposite transport of the β-amyloid in the brain is regulated by receptors for Advanced Glycated End Products (RAGEs). Activation of RAGEs by β-amyloid leads to pathological effects, such as proinflammatory activation of endothelial cells, their apoptotic death and decrease in cerebral blood flow with secondary damage of cells in the CNS. Proteolytic degradation of β-amyloid is controlled by neprilysin and the insulin-degrading enzyme (IDE). Expression of these enzymes fall during aging and diabetes mellitus. Moreover, dysfunctions in neuronal autophagy after β-amyloid accumulation were recognized as an additional important mechanism of AD development.

The β-amyloid theory of AD also has several discrepancies, because of the other than non-β-amyloid products of APP degradation may be involved in the pathogenesis of the disease. Nevertheless, inhibitors of secretases and immunization against APP were proposed with low efficacy as pathogenetic therapy of AD.

3. Protein τ (tau) hypothesis. The protein τ is highly soluble and relates to microtubules. It stabilizes them in physiologic conditions. Generally, microtubules perform supporting functions in cells; they also regulate axonal transport and neuronal growth. In the CNS protein τ presents in 6 isoforms, but in patients with AD it presents in hyperphosphorylated state, and in this state it aggregates with cytoskeletal proteins. Hyperphosphorylated protein τ is a component of neurofibrillary tangles together with β-amyloid. Neurobibrillary tangles impair axonal transport thus causing neurodegeneration. These tangles are detected in the amygdala and temporal, frontal and parietal cortical areas.
4. Oxidative stress is a component of "vicious circle" in AD, because it is initiated by β-amyloid and protein τ, and, in turn, augments them. Oxidative stress also damages neurons, stimulates their programmed and non-programmed cell death and provokes neuroinflammation. Different antioxidants are recommended for prevention of AD rather than treatment.
5. Impairment of calcium homeostasis. In AD it results from alteration of calcium-buffering capacities in neural cells, dysregulation of calcium channels activities, excitotoxicity, and disruption of mitochondrial functions. Accumulation of intracellular calcium leads to activation of calcium-dependent enzymes, oxidative stress, ATP deficiency, accumulation of β-amyloid and phosphorylation of protein τ and necrotic and/or apoptotic death of neurons.
6. Deficiency of neurotrophins. Directly infusion of neurotrophic growth factors is proposed now as a new antineurodegenerative strategy in AD.
7. Neuroinflammation (See above). Different novel anti-inflammatory strategies are tested now as a new approach to AD management.

Parkinson's disease

Parkinson's disease (PD) is a multifactorial progressive neurodegenerative disease affecting basal ganglia with corresponding symptoms (TRAP), which were described with the term "parkinsonism":

- **T** – tremor;
- **R** – rigidity;
- **A** – akinesia;
- **P** – postural disturbances.

In contrast to PD, parkinsonism is a result of toxic, traumatic, infectious or other diseases affecting basal ganglia, but unrelated to neurodegeneration. Parkinson's disease is a second most common neurodegenerative disease after AD in aging individuals. The disease was named in honor of James Parkinson, a British physician who first described these symptoms. Specific features of PD are neuronal loss in the substantia nigra, intracellular protein α-synuclein accumulation with formation of Lewy bodies and reactive gliosis. Genetic predisposition is common in familial PD. At least 20 genes-candidates were proposed as a cause of this disorder, but most common are mutated gene encoding α-synuclein, genes whose products control mitochondrial quality, proteins folding, membrane trafficking, autophagy, synaptic function, vesicle release, and ubiquitin-dependent proteasomal pathway. Pathogenesis of PD has common features with other neurodegenerative diseases (Fig. 8-7).

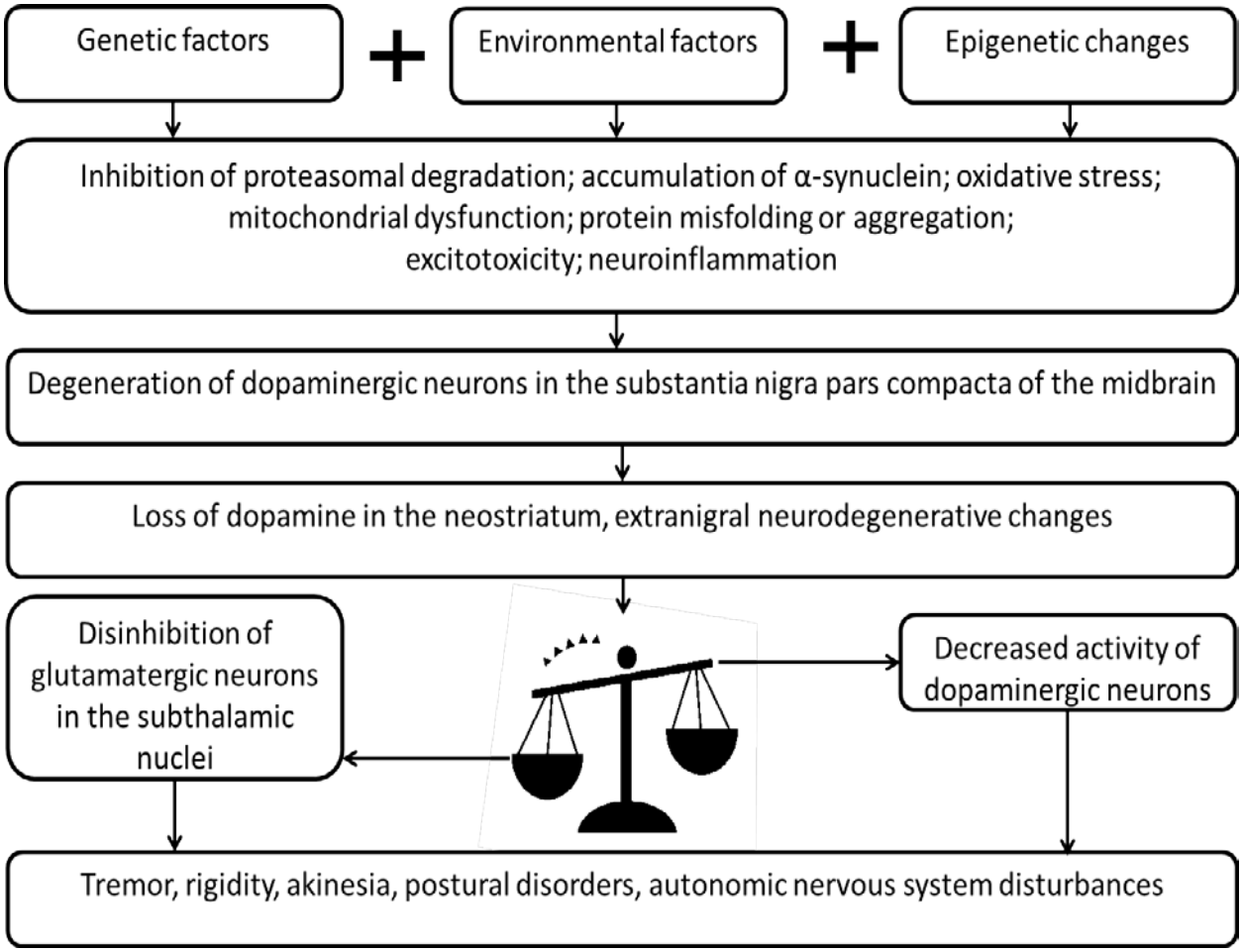


Figure 8-7. Simplified mechanisms of Parkinson's disease development

Presented basic pathogenetic mechanisms are not as a consequence of events, because in each separate case initiating process may differ. Moreover, all mechanisms summarized in the Fig. 8-7 influence each on other, thus creating multiple interrelated "vicious circles". As a result of these mechanisms, dopaminergic neurons in the substantia nigra die followed by extranigral neurodegenerative changes. The basal ganglia participate in the control of actions and goal-directed behavior.

Degeneration of dopaminergic neurons in the basal ganglia leads to predominated activity of cholinergic neurons, tremor and postural disturbances. Akinesia is explained by increased activity of GABA-mediated inhibitory pathways. Because the basal ganglia also controls activity of the autonomic nervous system, patients with PD will have some related disorders like as uncontrolled sweating, hypersalivation, dysphagia, ortostatic hypotension, abnormal thermoregulation, constipation, urine incontinence, and impotence. Later cognitive disturbances due to neurodegeneration in other areas of brain may appear.

Pathophysiological basis for Parkinson's disease management: (1) to decrease dopamine level dopamime analogs are used (levodopa is a "gold standard" of PD pharmacotherapy); (2) dopamine receptors agonists (bromocriptine, pramipexole, ropinirole, rotigotine); (3) monoaminoxidase inhibitors to prevent excessive dopamine degradation (selegiline, rasagiline); (4) to suppress hyperactivity of cholinergic neurons anticholinergic drugs are recommended (trihexyphenidyl, benztropine); (5) physiotherapy – deep brain stimulation; (6) psychotherapy, medical care, support and education; (7) stereotactic surgical treatment – thalamotomy and pallidotomy.

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder that affects the corticospinal tract, brainstem and anterior horn cells of the spinal cord. The term consists from two parts: "amyotrophic" indicates muscle atrophy after damage of motor neurons and "lateral sclerosis" means a loss of fibers in the lateral columns, fibrillary gliosis with steadfastness of the lateral columns. Leading symptoms include focal, then generalized weakness, paralysis and death due to respiratory failure. Over 60% of patients usually die within 3 years after diagnosis, because of there is no disease-modifying therapy for ALS currently. Incidence of ALS in general population is 2-3 case per 100.000 people. Most common ALS is a sporadic (in 90-95% of cases); familial ALS is rare (5-10% among all affecting patients). ALS is considered to be complex multifactorial disease. Genetic predisposition plays a more significant role in the pathogenesis of familial ALS with different types of inheritance of genes-candidates: autosomal dominant, autosomal recessive or X-linked. There are at least 23 genes-candidates, whose products are involved in the mechanisms of ALS development, but most common mutated genes in both familial and sporadic ALS are: chromosome 9 open reading frame 72 (C9orf72), fused in sarcoma gene (FUS), TAR DNA binding protein (TARDBP), and Cu/Zn SOD1. Products of first three genes participate in RNA metabolism, whereas mutated SOD1 gene results in oxidative stress.

Genetic predisposition act in combination with different environmental and intrinsic factors which increase susceptibility to ALS: toxins, smoking, tremendous physical exercises, occupation, dietary factors, immune dysregulation. Advanced age and male sex enhance susceptibility to ALS. Pathogenesis of ALS has several above-mentioned common among all neurodegenerative diseases mechanisms: oxidative stress, mitochondrial dysfunction, abnormal axonal transport, excitotoxicity, excessive protein aggregation, endoplasmic reticulum stress, abnormal RNA processing and neuroinflammation, abnormal micro-RNA expression and accelerated death of motor neurons. Accumulation of mutated proteins in neurons (SOD1, TDP-43, FUS and some others) results in stress response and caspase-dependent excessive death of neurons. Simplified natural history of ALS is depicted in the Fig. 8-8.

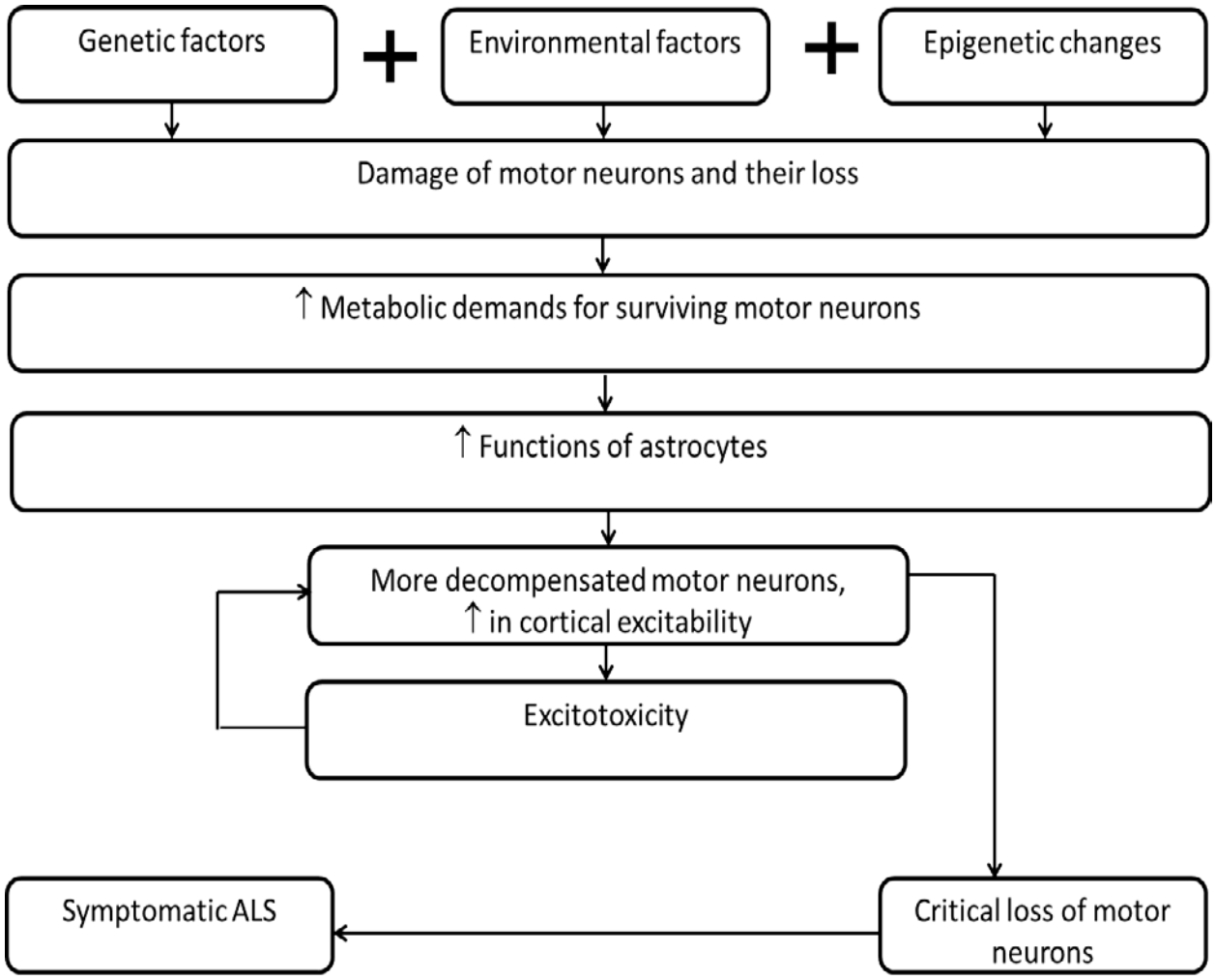


Figure 8-8. Natural history of ALS

Demyelinating diseases

Examples of these diseases are multiply sclerosis and acute disseminated encephalomyelitis. Common features of demyelinating diseases involve selective destruction of myelin in the CNS, inflammation and reactive gliosis.

Multiply sclerosis (MS) is an autoimmune inflammatory disorder, which is manifested morphologically by an appearance of myelin lesions and plaques in the white brain matter with progressive subsequent neuronal loss with defects in the gray matter at any part of the central nervous system appearing at any time. To better understand pathogenesis of the multiple sclerosis, it is desirable to repeat basic mechanisms of autoimmune disease development (See the Textbook "General pathophysiology: the essentials"). As for multifactorial disease, interactions at least of two groups of causative factors promote MS development. More than 150 genes-candidates were identified as a genetic base of the disease, at the same time most of them are related to HLA region of the chromosome 6: HLA-DR2, HLA-DQ6, DQA0102, DQB10602, HLA-DRB1, DR15, DRB1*1501, DRB1*1503. Genes encoding IL-7 and IL-2 receptor α also produce abnormal immune regulation. Polygenic type of inheritance seems to be an important trait of MS development rather than rare monogenic forms. Generally, most mutated genes associate with the presence of autoreactive lymphocytes and impaired antigens presentation. Environmental factors act in the cooperation of genetic predisposition. Different environmental factors provoke MS development: infections (especially *Epstein Barr virus, human herpes virus type 6*, *Mycoplasma pneumonia*); smoking; incorrect diet with high caloric intake and high meat intake; obesity; gut dysbiosis; vitamin B_{12} or D deficiency; smoking, and UV-radiation. Action of these factors results in DAMPs or PAMPs releasing, which, together with most important self-antigen in MS – myelin basic protein (MBP) are recognized by APCs, which produce IL-12, 23 and IL-4 with polarization of CD4+ T-lymphocytes into Th1, Th2 or TH17. Th1 and Th17 support inflammatory reaction via releasing of proinflammatory cytokines, whereas Th2 mediates anti-inflammatory response. Th2-derived cytokines stimulate B-lymphocytes to produce autoantibodies against different components of myelin. CD8+ (cytotoxic) lymphocytes induce apoptosis of glial cells and increase vascular permeability by perforin. Autoreactive lymphocytes also express Fas-L, which interacts with Fas-R on the surface of oligodendrocytes thus stimulating their apoptotic death. As a result, myelin synthesis falls.

Demyelination leads to conduction block, because of normally myelin provide salutatory impulses propagation through the nodes of Ranvier. Moreover, demyelination impairs trophic support for neurons with their damage and death; it also leads to the remodeling of gap junctions secondary to redistribution of ion channels. In response to neurons injury glial cells become activated and produce ROS and RNS potentiating excitotoxicity thus leading to secondary injury of axons and neurons. As a result, multiply sclerosis clinically exhibits weakness of limbs combined with other symptoms – spasticity, ataxia, visual abnormalities and even blindness, sensory disorders (paresthesias, hypesthesia), autonomic disorders, psychologic and cognitive disturbances. It is important to note, that at least 70% of axons in the lateral corticospinal tract die before detection of paraplegia usually.

Pathophysiological basis for multiple sclerosis management: (1) for treatment of acute MS to suppress inflammation glucocorticoids and plasma exchange

are used; (2) for disease-modifying therapy to reduce activity of MS are recommended: (a) IFN-β analogs, which decrease expression of MHC molecules on the surface of APCs thus impairing antigens presentation, reduce synthesis of proinflammatory cytokines and augment production of regulatory cytokines, suppress proliferation of self-reactive T-lymphocytes and diminish their accumulation in the CNS; (b) mixture of L-amino acids (glutamine, lysine, alanine and tyrosine) – glatiramer acetate, which stimulates formation of antigen-specific suppressor T-lymphocytes, binds with MHC molecules thus preventing their interaction with MBP and restores synthesis of regulating cytokines; (c) monoclonal antibody against the α4 subunit of the α4β1 lymphocytic integrin natalizumab, which suppresses entry of lymphocytes in the CNS; (3) symptomatic therapy. Novel approaches are tested now: monoclonal antibodies against CD20 of B-lymphocytes, against IL-2 receptor or against CD52; sphingosine-1-phosphate receptor antagonists retaining lymphocytes in the secondary lymphoid organ; MBP to induce immune tolerance; bone marrow transplantation and stem cell therapy.

Disorders of the autonomic nervous system

The peripheral autonomic nervous system (ANS) consists of three divisions: the sympathetic nervous system (SNS), the parasympathetic nervous system (PNS) and the enteric nervous system (ENS) and regulate almost all vital functions. Effects of the SNS and PNS system activation are summarized in the Table 8-4 for future discussion of the autonomic disorders. Hence, disorders of the ANS manifest by symptoms related to excessive or inadequately low activity of the SNS or PNS.

Table 8-4. Main effects of the SNS and PNS activation

Organ, function	Sympathetic nervous system	Parasympathetic nervous system
Pupil of the eye	Mydriasis (α_1)	Miosis
Heart		
Heart rate	↑ (β_1)	↓
Myocardial contractility	↑ (β_1, β_2)	↓
Velocity of impulses conduction	↑ (β_1, β_2)	↓
Coronary arteries tone	↑ (α_1, α_2); ↓ (β_2)	-
Skin		
Arterioles tone	↑ (α_1, α_2)	-
Sweat glands secretion	Slightly ↑ (α_1)	
Arterioles tone in skeletal muscles	↑ (α_1); ↓ (β_2, M)	-
Bronchial muscles tone	↓ (β_2)	↑
Stomach and intestine		
Motility and tone	↓ (α_1, α_2, β_2)	↑
Tone of sphincters	↑ (α_1)	↓
Secretion	↓	↑

Urinary bladder Sphincter tone Detrusor tone	 ↑ ↓	 ↓ ↑
Uterus Myometrium tone	↑ in pregnancy (α_1); ↓ (β_2)	Variable
Male sex organs	Ejaculation (α_1)	Erection
Secretion of salivary glands	Thick, viscous secrete	Profuse, watery-like secrete

Disorders of the ANS may result from damage of the central or peripheral nervous system; they may be inherited or acquired. Central causes of the ANS disorders are subdivided into those, which are associated with multisystem degeneration (for instance, multiple system atrophy, Parkinson's disease) or not (caused by frontal cortex lesion of any etiology, disorders of the limbic system, hypothalamic disorders, diseases affecting brain stem and cerebellum). Spinal cord disorders also may lead to the autonomic disturbances. Such situations are seen in patients with the spinal cord trauma, syringomyelia, multiple sclerosis, amyotrophic lateral sclerosis, tetanus, and tumors of the spinal cord. Next groups of ANS disorders are autonomic peripheral neuropathies, which affect both myelinated and unmyelinated nerve fibers of the sympathetic and parasympathetic nerves. Peripheral autonomic neuropathies may manifest suddenly and may be alleviated (for example as an autoimmune disorder in paraneoplastic autonomic neuropathy, Guillain-Barré syndrome, botulism, porphyria and after some drugs (opioids, some selective serotonin reuptake inhibitors, some antihypertensives, tricyclic antidepressants, decongestants, some diuretics, etc.) and toxins (alcohol, cocain, organophosphates) exposure or may persist for a long time in patients with amyloidosis, diabetes mellitus, autoimmune diseases and some familial syndromes.

Common symptoms include orthostatic hypotension due to loss of baroreflex response, arrhythmias, hyperhidrosis or anhydrosis, bowel disorders, bladder dysfunction, impotence, and disorders of thermoregulation.

Disorders of the peripheral nervous system

The peripheral nervous system includes cranial nerves, dorsal and ventral spinal roots, ganglia, spinal nerves and their continuations. Peripheral nerves carry somatic sensory, somatic motor, visceral sensory and autonomic fibers. Peripheral nerve may be myelinated or non-myelinated. Myelin is a product of Schwann cell's plasmalemma and a pre-requisite for saltatory nerve conduction. Basic reactions of peripheral nerve fibers to injury are illustrated in the Fig. 8-9. In contrast to CNS, peripheral nerves have capacity to axonal regeneration and remyelination.

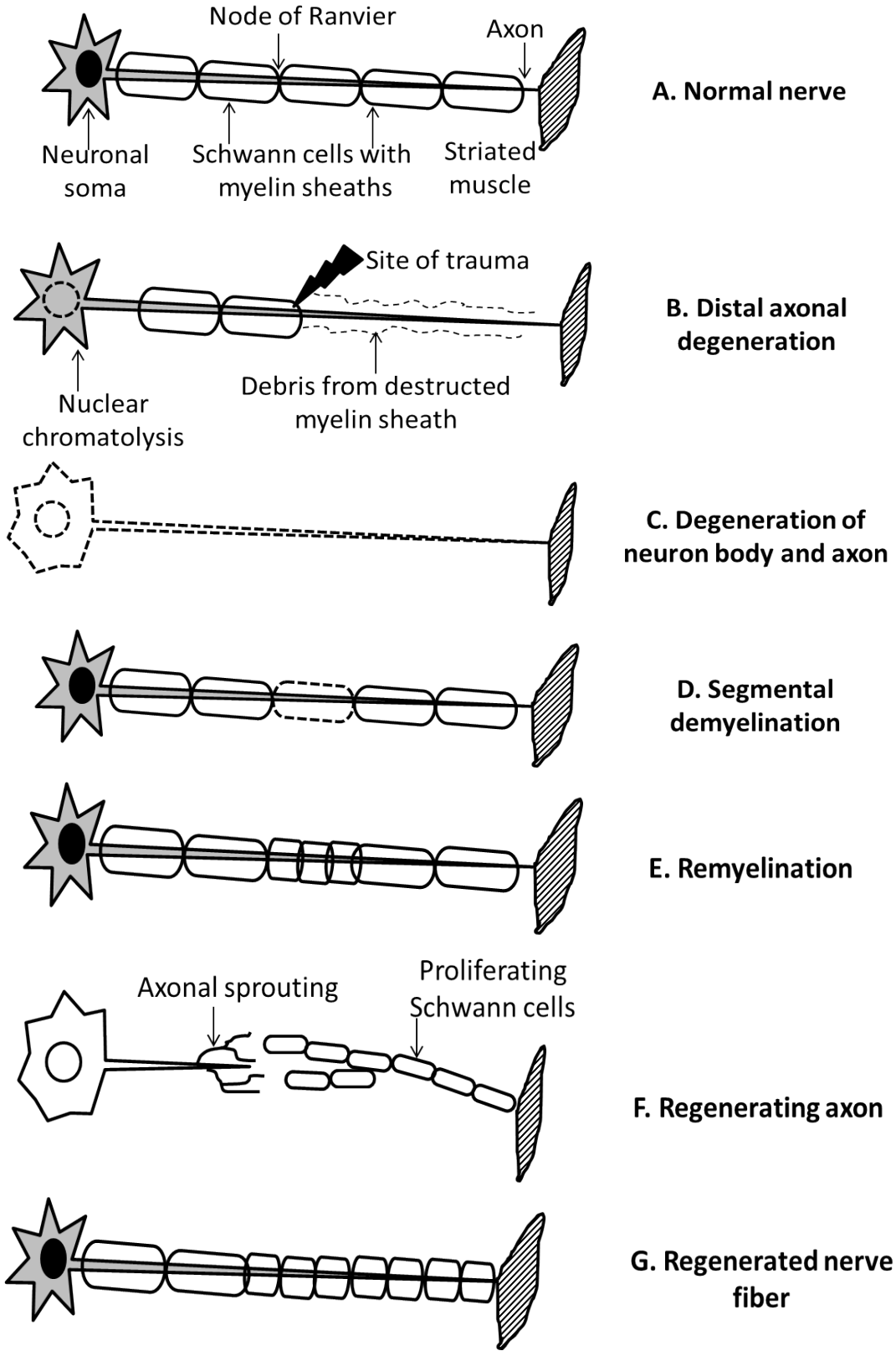


Figure 8-9. Types of peripheral nerve response to injury

Axonal degeneration is a consequence of neuronal body or axon damage. In case of axon fibers damage, axonal degeneration is thought to be distal. Distal ax-

onal degeneration is commonly seen in different neuropathies. The neuronal soma and proximal part of axon initially stay intact. Axonal regeneration and restoration of nerve function are possible, if underlying cause of distal axonal degeneration was removed. Axonal degeneration also may occur after primary damage of neuronal cell body, for instance, in patients with poliomyelitis. In such cases potential for nerve recovery is limited. A particular kind of axonal degeneration is called Wallerian degeneration, which develops distal to nerve transection or crush injury.

Demyelination is characterized by a loss of myelin from one or more internodes along myelinated fiber due to Schwann cell dysfunction. Macrophages infiltrate perineural space and phagocytose myelin debris. Compensatory, in response to demyelination several processes develop usually: proliferation of Schwann cells, remyelination of demyelinating segments and recovery of function.

Most common disorder affecting peripheral nervous system is peripheral neuropathy. Peripheral neuropathies could affect one selected or several nerves (mononeuropathy or polyneuropathy, accordingly); they also may be hereditary or acquired; with predominantly axonal neuropathy, demyelinating neuropathy, or mixture form. Etiology of different neuropathies is listed in the Table 8-5.

Clinically, peripheral neuropathies manifest by muscle weakness, muscle atrophy, sensitivity disorders, and autonomic dysfunction. As a rule, nerve conduction velocity is significantly decreased in demyelinating neuropathies and near to normal in axonal neuropathies.

Table 8-5. Etiology and pathogenesis of neuropathies

Groups	Diseases	Particular features
Hereditary		
Charcot-Marie-Tooth disease (CMT)	Includes several types	Different type of inheritance (dominant, recessive or sex-linked); extensive demyelination, distal axonal degeneration. Patients have normal lifespan usually.
Porphyric neuropathy	Porhyrias	Pathogenesis is unknown; heme deficiency may lead to neurological dysfunction.
Acquired		
Autoimmune-mediated	Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy) and chronic demyelinating polyneuropathy	Pathogenesis relates to general principles of autoimmunity development; demyelination and perivascular lymphocytic infiltration are common. Plasmapheresis is a treatment of choice.

Metabolic	Diabetic polyneuropathy	Activation of polyol and hexosamine pathways of glucose metabolism, activation of protein kinase C, oxidative stress, ↑ AGEs; obstruction of vasa nervorum, demyelination and inadequate nerve regeneration due to poor production of neurotrophic factors. Treatment is based in the correction of sugar level in the blood, symptomatic treatment and education.
	Uremic neuropathy	Distal axonal degeneration and demyelination; full mechanisms are unknown. The disorder is preventable and treatable by dialysis or kidney transplantation.
	Hypothyroid neuropathy	Distal axonal degeneration and demyelination are main hallmarks.
	Hepatic neuropathy	It is a relatively rare complication of chronic liver failure; it relates to vitamin deficiency or alcohol intake commonly.
	Critical care neuropathies	Associated with sepsis and multiorgan failure; in rare cases are due to axonal degeneration; in most cases are explained by primary myopathies rather than neuropathies. Disorders are potentially correctable.
Nutritional	Alcoholic neuropathy	Basic mechanisms are: abnormal absorption of vitamins related to B group; abnormal myelin formation and demyelination; oxidative stress; toxic effects of ethanol. Neuropathy is axonal in origin with secondary demyelination.
	Beri-beri neuropathy (thiamine deficiency)	Normally vitamin B_1 participates in the neuromuscular transmission. Neuropathy is resulted from axonal degeneration and demyelination.
	Related to vitamin B_{12} deficiency	Demyelination of peripheral nerves, posterior and lateral columns of spinal cord, and nerves within the brain may occur due to abnormal myelin synthesis and oxidative-mediated nerves injury.
	Related to vitamin E deficiency	Neuronal degeneration due to oxidative stress produces peripheral neuropathies, ophthalmoplegia, and destruction of pos-

		terior columns of spinal cord.
	Complicated postgastrectomy state	Related to malabsorption of both water-soluble and fat-soluble vitamins
	Related to celiac disease	May associate with autoimmunity
Vasculitic neuropathies	Systemic vasculitis related to polyarteriitis nodosa, rheumatoid arthritis, Wegener's granulomatosis, Sjögren's syndrome and vasculitis complicated different infections	Occlusion of large arteries or vasa nervorum supplying nerves results in axonal degeneration.
Toxic neuropathies	Intoxication with environmental agents (metals – arsenic, lead, mercury, thallium; industrial poisons), substance abuse (alcohol, glue inhalation, nitrous oxide inhalation) or drugs (amiodarone, antiviral drugs, cisplatin, gold, isoniazid, nitrofurantoin, etc.)	Basic mechanism is toxic-mediated axonal degeneration. The key of treatment is prompt recognition of toxin and its withdrawal.
Paraneoplastic neuropathy	Related to different form of cancer	Pathogenesis is not fully understood; manifests by distal sensoriomotor polyneuropathy, subacute sensory polyneuropathy, subacute motor polyneuropathy and inflammatory demyelinating neuropathy.
Amyloid neuropathy	Hereditary or acquired amyloidosis	Caused by deposition of amyloid in peripheral nerve and sensory and autonomic ganglia in perineural and perivascular space with subsequent mechanical peripheral nerves and ganglia damage.
Paraproteinemic neuropathy	Monoclonal gammopathies (Ig M, IgG, IgA-associated)	Some IgM monoclonal proteins react with sugars of the myelin-associated glycoprotein, a specific protein of Schwann cells with subsequent demyelination. Mechanisms of neuropathies caused by IgG and IgA are unknown.
Associated with infections	Herpes zoster, leprosy, AIDS, cytomegalovirus infection, diphtheria, Lyme disease (borreliosis)	Manifests by mono- or polyneuropathies, often ganglia are involved

Mechanical / compressive	Examples are: median nerve compression with carpal tunnel syndrome, ulnar nerve compression in the hand with cubital tunnel syndrome, etc.	Associates with sensory and motor disorders
Cryptogenic neuropathy	Etiology is unknown	Manifests by chronic axonal neuropathy

SUPPLEMENT

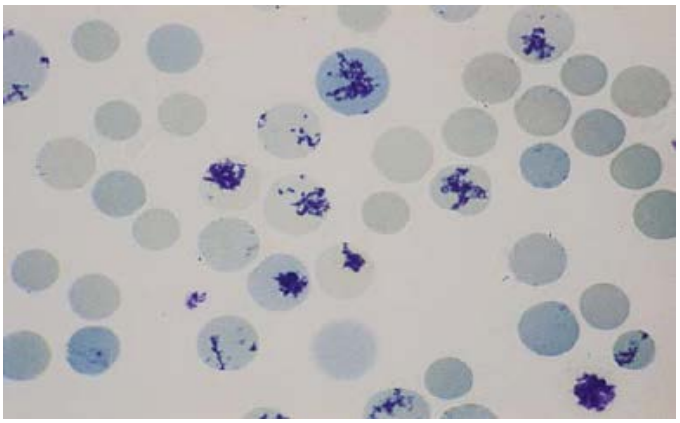


Figure 1-2. Reticulocytosis following acute hemorrhage

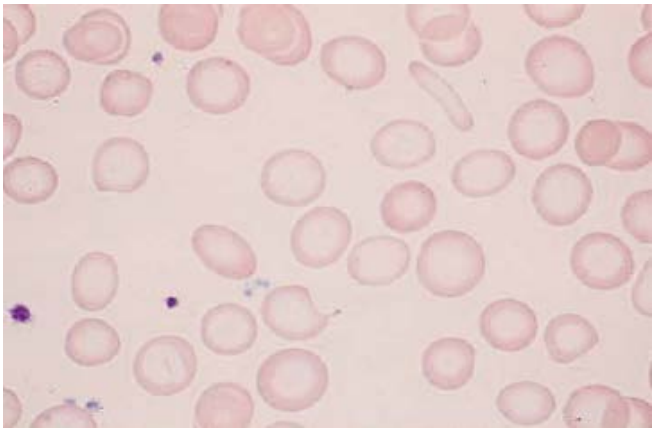


Figure 1-5. Peripheral blood smear during iron deficiency anemia

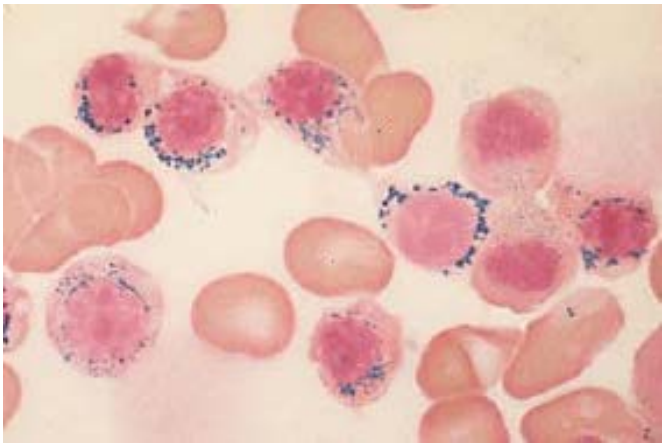


Figure 1-9. Ring sideroblasts in the bone marrow smear

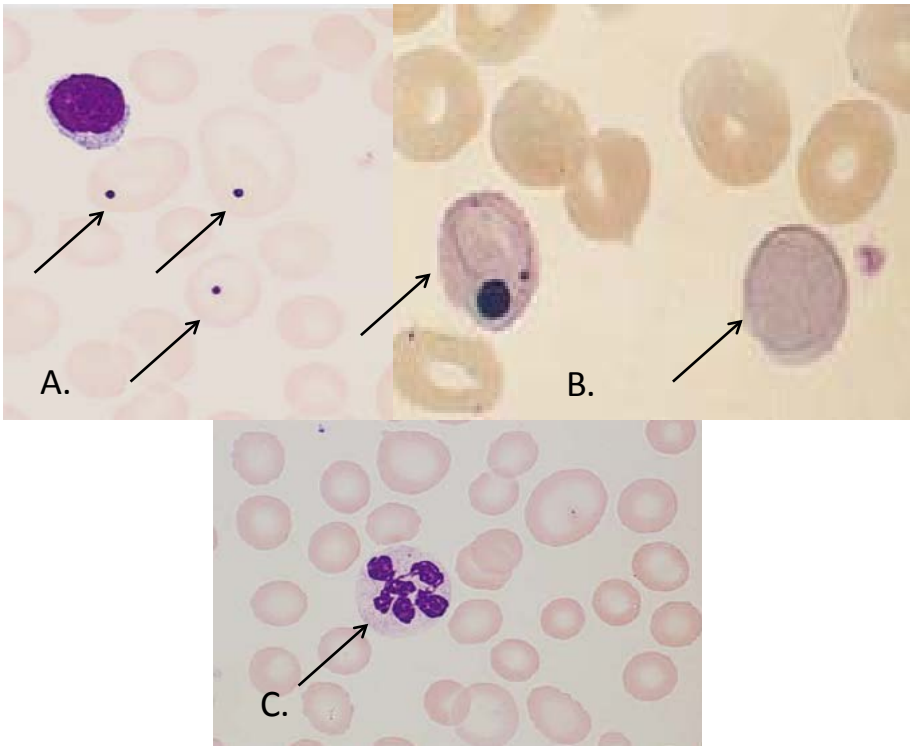
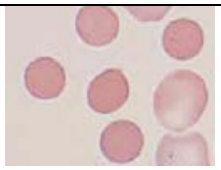
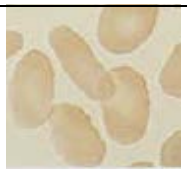
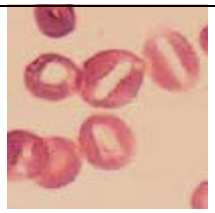


Figure 1-11. Blood smear in vitamin B_{12}-deficiency anemia

Arrows show on: A) three megalocytes with Howell-Jolly bodies; B) erythrocytes with Cabot ring; C) hypersegmented neutrophil

Table 1-10. Selected hereditary membranopathies

Disease	Defect	Pathogenesis	Peripheral blood smear	Treatment
Hereditary spherocytosis	Defects in RBCs' membrane proteins spectrin, ankyrin, band 3 and protein 4.2	Membrane instability, membrane loss, osmotic swelling→destruction of poorly deformable RBCs in the spleen, extravascular hemolysis	 Micro-spherocytes	Blood transfusions, splenectomy
Hereditary elyptocytosis	Defects in RBCs' membrane proteins spectrin, ankyrin, protein 4.1 and glycophorin C	Dysruption of RBCs' cytoskeleton, poor deformability in the spleen, extravascular hemolysis	 Ellyptocytes	Blood transfusions, splenectomy in severe cases

Hereditary stomatocytosis	Molecular bases are unknown	Disturbances of water and electrolyte balance in RBCs, ↑ osmotic fragility	 Stomatocytes	Splenectomy; ↑ risk of thrombosis after splenectomy

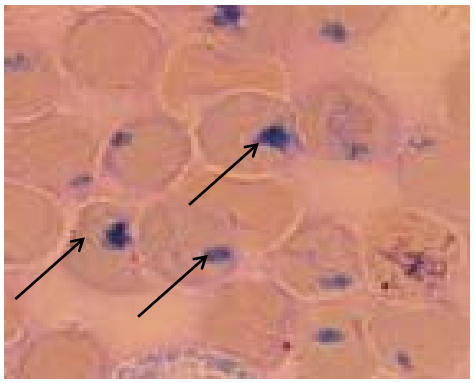


Figure 1-13. Heinz bodies (Nile blue sulfate staining) in patient with glucose-6-phoshate deficiency

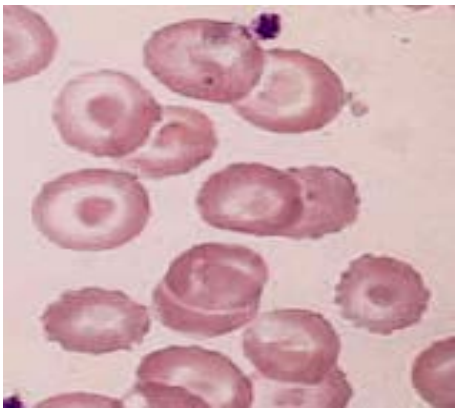


Figure 1-14. Target cells in thalassemia major

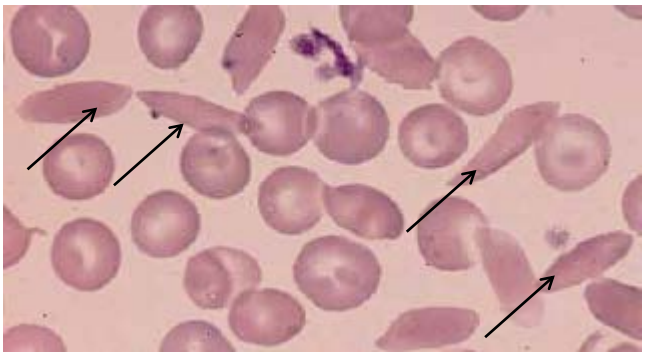
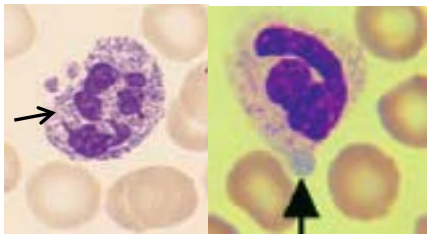


Figure 1-16. Sickle erythrocytes



A) B)

Figure 1-20. Toxic inclusions in granulocytes: A) vacuoles; B) Döhle body

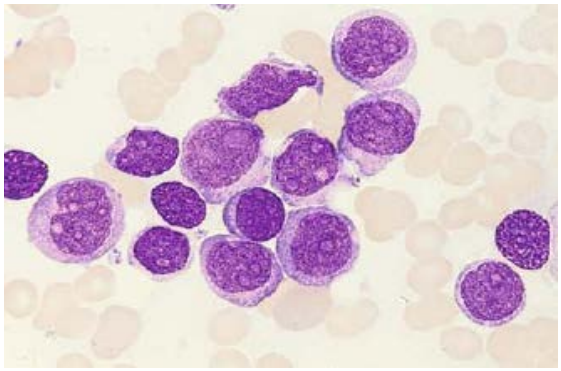


Figure 1-22. Acute myeloblastic leukemia

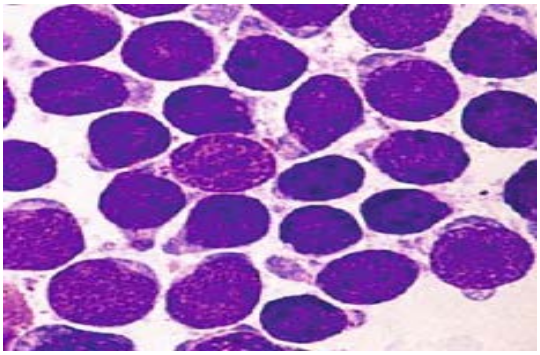


Figure 1-23. Acute lymphoblastic leukemia

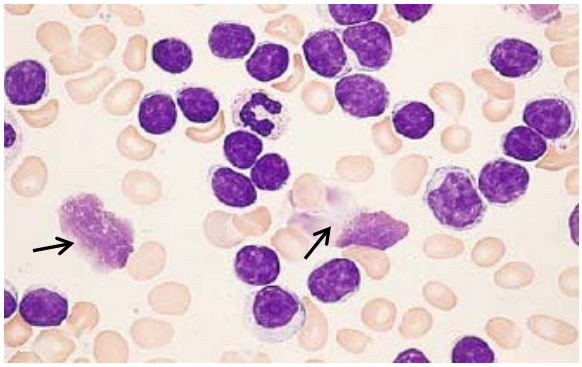


Figure 1-24. Chronic lymphoid leukemia
Arrows show on Gumprecht shadows (“smudge cells”)

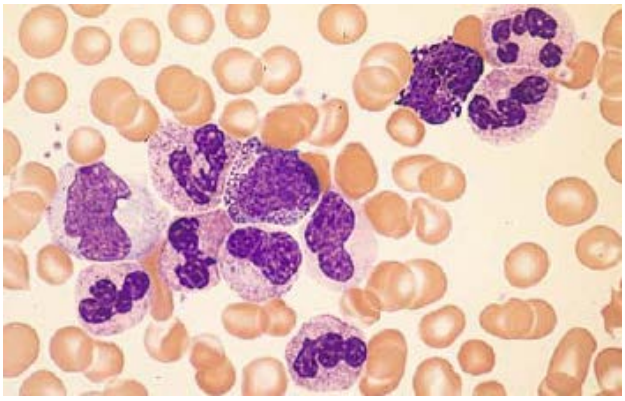


Figure 1-25. Chronic myeloid leukemia

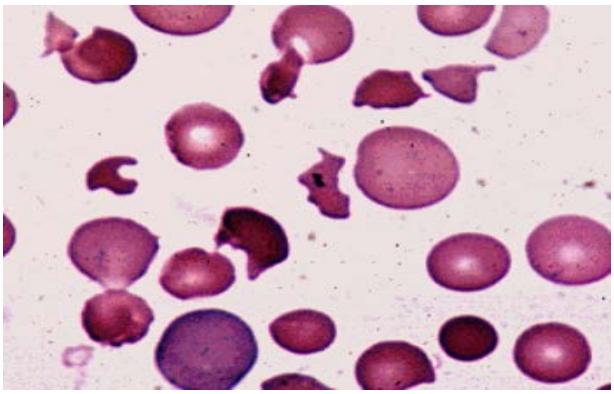


Figure 1-30. Fragmented RBCs (shistocytes) in the peripheral blood in patient with DIC

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КЛИНИЧЕСКАЯ ПАТОФИЗИОЛОГИЯ: ОСНОВЫ

CLINICAL PATHOPHYSIOLOGY: THE ESSENTIALS

Пособие
на английском языке

Редактор Л.Е. Беляева
Технический редактор И.А. Борисов
Компьютерная верстка Л.Е. Беляева

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